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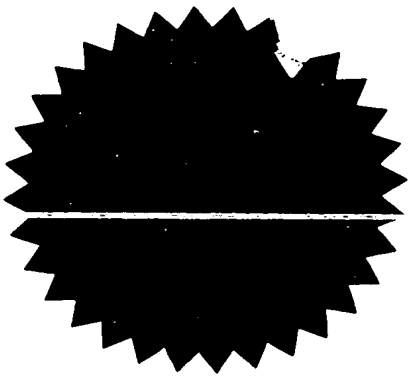

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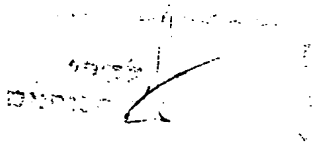

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Application for Patent

C:25905

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NEW TECHNOLOGIES (SA-YSY) LTD.
15 Bat Galim Avenue
P.O. Box 8044
Haifa 31080

טכנולוגיות חדשות (סע-ישי) בע"מ
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ELECTRICAL MUSCLE CONTROLLER

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C:25905

טכנולוגיות חדשות (סע-ישי) בע"מ

ELECTRICAL MUSCLE CONTROLLER

FIELD OF THE INVENTION

The present invention relates to cardiac muscular control, in particular control using non-excitatory electrical signals.

BACKGROUND OF THE INVENTION

The heart is a muscular pump whose activation is controlled by electrical stimulation of the cardiac muscle. In a normal heart, an activation signal is generated in the right atrium of the heart, conducted to the left atrium of the heart and after a delay, conducted to the left ventricle and the right ventricle. Since the electrical resistance of the heart muscle is relatively high, the activation signal is not merely conducted from muscle cell to muscle cell. Rather, each muscle cell generates a new action potential for stimulating the next cell, after a short delay and in response to the activation signal which reaches it.

In a ventricle cardiac muscle cell, the resting voltage potential across its cellular membrane is approximately -90 millivolts (the inside is negatively charged with respect to the outside). Fig. 1A shows an action potential of a ventricle cardiac muscle cell during the cardiac cycle. When an activation signal reaches one end of the cell, a depolarization wave rapidly advances along the cellular membrane until the entire membrane is depolarized, usually to approximately +20 millivolts (23). Complete depolarization of the cell membrane occurs in a very short time, such a few millisecond. After the rapid depolarization, the cell slowly repolarizes by about 20 millivolts over a period of approximately 200-300 milliseconds, called the plateau (25). It is during the plateau that the muscle contraction occurs. At the end of the plateau, the cell rapidly repolarizes (27) to its resting potential (21). Different cardiac muscle cells have different electrical characteristics, in particular, cells in an SA node do not have a substantial plateau and do not reach as high a resting potential as ventricular cells.

In the following discussion, it should be appreciated that the exact mechanisms which govern action potentials and ionic pumps and channels/gates are not precisely known. Many theories exist and the field in is a constant state of flux.

The electrical activity mirrors chemical activity in the cell. In a cell before depolarization, the concentration of sodium ions inside the cell is about one tenth the concentration in the interstitial fluid outside the cell. Potassium ions are about thirty-five times more concentrated inside the cell than outside. Calcium ions are over ten thousand times more concentrated outside the cell than inside the cell. These concentration differentials are maintained by the selective permeability of the membrane to different ions and by ionic pumps in the membrane of the cell which continuously pump sodium and calcium ions out and potassium ions in. One result of the concentration differences between the cell and the environment external to the cell is a large negative potential in the cell, about 90 millivolts as indicated above.

When a portion of the cell membrane is depolarized, such as by an action potential, the depolarization wave is spread along the membrane and this wave causes a plurality of voltage-

gated sodium gates to open. An influx of sodium through these gates rapidly changes the potential of the membrane from negative to positive (23 in Fig. 1A). Once the voltage becomes less negative, these gates begin to close, and do not open until the cell is again depolarized. It should be noted that many sodium gates require a negative voltage of at least a particular value in order to be primed for reopening. Thus, these gates cannot be opened by an activation potential before the cell has sufficiently repolarized. In most cells, the sodium gates usually close more gradually than they open. During the plateau stage (25 in Fig. 1A), voltage-gated potassium gates and voltage-gated calcium gates open. Potassium then flows out of the cell, to repolarize it, and calcium flows into the cell to activate the muscle proteins. In general, the flow of potassium and calcium is many times slower than the flow of the sodium, which is the reason why the plateau lasts so long. According to some theories, the potassium gates may also open as a result of the action potential, however, the probability of a potassium gate opening is dependent on the potential. Thus, many gates open only after the depolarization of the cell is under way or completed. Possibly, the potassium channels are be activated by the calcium ions. In addition, some of the potassium channels are triggered by the repolarization of the membrane. The calcium gates also conduct sodium back into the cell, which helps extend the plateau duration.

Some theories hypothesize that the calcium influx into the muscle cell triggers the release of intra-cellular calcium stores. In this theory, the effect of calcium influx is magnified by the intra-cellular calcium stores. However, the response of these calcium stores may be bell-shaped, so that too great an influx of calcium may reduce the amount of available calcium relative to amount made available by a smaller influx.

While the cell is repolarizing (25, 27 in Fig. 1A), it enters a state of hyper polarization, during which the cell cannot be stimulated again to fire a new action potential. This state is also called the refractory period. The refractory period is divided into two parts. During an absolute refractory period, the cell cannot be stimulated to fire a new action potential no matter what the signal is. During a relative refractory period, a much larger than usual stimulus signal is required to cause the cell to fire a new action potential. This state is probably caused by the potassium gates remaining open. Another probable cause is that the sodium gates must be primed by a negative voltage, so the cell membrane cannot be depolarized by flow of sodium ions until it is sufficiently repolarized. Once the cell returns to its resting potential (21), the cell may be depolarized again.

It is known that by applying a positive potential across the membrane, a cell may be made more sensitive to activation signal. Some cells in the heart, such as the cells in the SA node (the natural pacemaker of the heart) have a resting potential of about -55 millivolts. As a result, their voltage-gated sodium gates are permanently inactivated and the depolarization stage (23) is slower than in ventricular cells. However, cells in the SA node have a built-in leakage current, which causes a self-depolarization of the cell on a periodic basis. In general, it appears that when the potential of a cell stay below about -60 millivolts for a few milliseconds, the voltage-gated

sodium gates are blocked. Applying a negative potential across its membrane make a cell less sensitive to activation and also hyper-polarizes the cell membrane, which seems to reduce conduction velocity.

In an experimental methodology called voltage clamping, an electrical potential is maintained across at least a portion of a cell membrane to study the effects of voltage on ionic channels, ionic pumps and on the reactivity of the cell.

It should be appreciated that, activation signals are propagated within the heart by sequentially activating connected muscle fibers. Regular electrical currents can be conducted in the heart, using the electrolytic properties of the body fluids, however, due the relatively large resistance of the heart muscle, this conduction cannot be used to transmit the activation signal.

In modern cardiology many parameters of the heart's activation can be controlled. Pharmaceuticals can be used to control the excitability, contractility and duration of the refractory periods in the heart. These pharmaceuticals may be used to treat arrhythmias, prevent fibrillations and modulate the heart contractility. A special kind of control can be achieved using a pacemaker. A pacemaker is an electronic device which is typically implanted to replace the heart's electrical excitation system or to bypass a blocked portion of the conduction system. In some types of pacemaker implantation, portions of the heart's conduction system, for example an AV node, must be ablated in order for the pacemaker to operate correctly. Another type of electronic device is a defibrillator. As an end result of many diseases, the heart may become more susceptible to fibrillation, in which the activation of the heart is substantially random. A defibrillator senses this randomness and resets the heart by applying a high voltage impulse(s) to the heart.

Pharmaceuticals are generally limited in effectiveness in that they affect both healthy and diseased segments of the heart, usually, with a relatively low precision. Electronic pacemakers, are further limited in that they are invasive, generally require destruction of heart tissue and are not usually optimal in their effects. Defibrillators have substantially only one limitation. The act of defibrillation is very painful to the patient and traumatic to the heart.

"Electrical Stimulation of Cardiac Myoctes," by Ravi Ranjan and Nitish V. Thakor, in Annals of Biomedical Engineering, Vol. 23, pp. 812-821, published by the Biomedical Engineering Society, 1995, the disclosure of which is incorporated herein by reference, describes several experiments in applying electric fields to cardiac muscle cells. These experiments were performed to test theories relating to electrical defibrillation, where each cell is exposed to different strengths and different relative orientations of electric fields. One result of these experiments is that if a defibrillation shock is applied during repolarization, the repolarization time is extended. In addition, it was discovered that cells have a preferred polarization. Cardiac muscle cells tend to be more irregular at one end than at the other. It is theorized in the article that local "hot spots" of high electrical fields are generated at these irregularities and that these "hot spots" are the sites of initial depolarization within the cell, since it is at these locations that

the threshold for depolarization is first reached. This theory also explains another result, namely that cells are more sensitive to electric fields in their longitudinal direction than in their transverse direction, since the irregularities are concentrated at the cell edges. In addition, the asymmetric irregularity of the cells may explain results which showed a preferred polarity of the applied electric field.

SUMMARY OF THE INVENTION

It is an object of some aspects of the present invention to provide a method of locally controlling the electrical and mechanical activity of cardiac muscle cells. Preferably, continuous control is applied. Alternatively, discrete control is applied. Further preferably, the control may be varied between cardiac cycles. One example of electrical control is shortening the refractory period of a muscle fiber by applying a negative voltage to the outside of the cell. The cell may be totally blocked from reacting by maintaining a sufficiently positive voltage to the outside of the cell, so that an activation signal fails to sufficiently depolarize the cellular membrane. One example of mechanical control includes, extending or shortening the plateau duration by applying voltage potentials across the cell, thus, increasing or decreasing the strength of contraction and the duration of the contraction.

It should be appreciated that some aspects of the present invention are different from both pacemaker operation and defibrillator operation. A pacemaker exerts excitatory electric fields over many cycles, while a defibrillator does not repeat its applied electric field over many cycles, due to the disruptive effect of the defibrillation current on the heart. In fact, the main effect of the defibrillation current is to momentarily stop all activity in the heart. It is a particular aspect of some embodiments of the present invention that the regular activation of the heart is not disrupted, rather, the activation of the heart is controlled, over a substantial number of cycles, by varying parameters of the reactivity of segments of cardiac muscle cells. In some aspect of the invention, the control is initiated as a response to an unusual cardiac event, such as the onset of fibrillation or the onset of various types of arrhythmias. However, in other aspects of the present invention, the control is initiated in response to a desired increase in cardiac output or other long-term effects, such as reducing the probability of ventricular fibrillation (VF) or increasing the coronary blood flow.

It is a further object of some aspects of the present invention to provide a complete control system for the heart which includes controlling the pacing rate, refractory period, conduction velocity and mechanical force of the heart. Except for heart rate, each of these parameters may be locally controlled, i.e., each parameter will be controlled in only a segment of cardiac muscle. It should be noted that heart rate may also be locally controlled, especially with the use of fences which isolate various heart segments from one another, however, in most cases this is detrimental to the heart's pumping efficiency.

In one preferred embodiment of the present invention, electrical and/or mechanical activity of a segment of cardiac muscle is controlled by applying a non-exciting voltage across the segment. A non-exciting voltage may cause an existing action potential to change, but it will not cause a new action potential, such as those induced by pacemakers. However, the non-exciting voltage may affect a later action potential, for example, it may delay such a potential or may facilitate it. Another type of non-exciting voltage is a voltage which does not cause a new contraction of the cardiac muscle cell to which the voltage is applied. Activation potential

generation may be averted either by the applied voltage being of the wrong polarity, being applied when the cell and/or the surrounding cells are not sensitive to it or by the amplitude of the voltage being too small to depolarize the cell to the extent that an action potential will be generated. Optionally, this control is exerted in combination with a pacemaker which applies an exciting voltage to the heart. In a preferred embodiment of the invention, a pacemaker (or a defibrillator) incorporates a controller, operating in accordance with at least one embodiment of the invention. A pacemaker and a controller may share a power supply, a micro-controller, sensors and possibly electrodes.

In another preferred embodiment of the present invention, arrhythmias and fibrillation are treated using fences. Fences are segments of cardiac muscle which are temporarily inactivated using electrical fields. In one example, atrial fibrillation is treated by channeling the activation signal from an SA node to an AV node by fencing it in. In another example, fibrillations are damped by fencing in the multitude of incorrect activation signals, so that only one path of activation is conducting. In still another example, ventricular tachycardia or fibrillation is treated by dividing the heart into insulated segments, using electrical fields and deactivating the fences in sequence with a normal activation sequence of the heart, so that at most only one segment of the heart will be prematurely activated.

In still another preferred embodiment of the invention, the muscle mass of the heart is redistributed using electrical fields. In general, changing the workload on a segment of cardiac muscle activates adaptation mechanisms which tend to change the muscle mass of the segment with time. Changing the workload may be achieved in accordance with a preferred embodiment of the invention directly by increasing or decreasing the plateau duration of the segment, using applied electrical fields. Alternatively or additionally, the workload may be changed in accordance with a preferred embodiment of the invention indirectly by changing the activation time of the activation sequence in the segment of the heart. Further additionally of alternatively, the workload may be changed by directly controlling the contractility of a segment of the heart.

In yet another preferred embodiment of the invention, the operation of the heart is optimized by changing the activation sequence of the heart and/or by changing plateau length at segments of the heart and/or by changing the contractility.

In still another preferred embodiment of the invention, the cardiac output is modified, preferably increased, by applying a non-excitatory electric field to a segment of the heart, preferably the left ventricle. Preferably, the extent of increase in cardiac output is controlled by varying the size of the segment of the heart to which such a field is applied. Alternatively or additionally, the strength of the electric field is changed. Alternatively or additionally, the timing of the pulse is changed. Alternatively or additionally, the duration of the pulse is changed.

In still another preferred embodiment of the invention, the developed ventricular pressure is modified, preferably increased, by applying a non-excitatory electric field to a segment of the heart, preferably the left ventricle. Preferably, the extent of increase in cardiac output is

controlled by varying the size of the segment of the heart to which such a field is applied. Alternatively or additionally, the strength of the electric field is changed. Alternatively or additionally, the timing of the pulse is changed. Alternatively or additionally, the duration of the pulse is changed.

In accordance with yet another preferred embodiment of the invention, the afterload of the heart is increased by applying non-excitatory electric fields to at least a segment of the heart, thereby, the flow in the coronary arteries is improved.

In accordance with another preferred embodiment of the invention various cardiac parameters are controlled via inherent cardiac feedback mechanisms. In one example, the heart rate is controlled by applying a non-exciting voltage to pacemaker cells of the heart, at or near the SA node of the heart. Preferably, the heart rate is increased by applying the non-excitatory field.

In a preferred embodiment of the invention, a single field is applied to a large segment of the heart, preferably, the field is applied at a time delay after the beginning of the systole. Preferably, the non-exciting field is stopped before half of the systole is over, to reduce the chances of fibrillation.

In another preferred embodiment of the invention, a plurality of segments of the heart are controlled, each with a different non-excitatory electric filed. Preferably, each electric field is synchronized to the local activation time or other local parameters, such as initiation of contraction. A further preferred embodiment of the invention takes into account the structure of the heart. The heart muscle is usually disposed in layers, with each layer having a (different) muscle fiber orientation. In this embodiment, a different field orientation and/or polarity is preferably applied for different orientations of muscle fibers.

In one preferred embodiment of the invention, this technique which takes the muscle fiber orientation into account may be applied to local defibrillation-causing electric fields, the purpose of which fields may be to delay the repolarization of a certain, limited segment of the heart, thereby creating a fence.

There is therefore provided in accordance with a preferred embodiment of the invention, a method of controlling a segment of cardiac muscle including sensing an activation time of the segment and applying a non-exciting electric field to the segment at a time delay after the activation time, for a given time duration. Preferably, this controlling of cardiac muscles used to increase the plateau duration of the segment and/or increase the contractility thereof.

There is also provided in accordance with another preferred embodiment of the invention a method of controlling a segment of cardiac muscle, including, providing at least one electrode near the muscle segment and electrifying the at least one electrode to apply non-exciting electric fields to the muscle segment.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be more clearly understood from the detailed description of the preferred embodiments and from the attached drawings in which:

Fig. 1A is a schematic graph of a typical cardiac muscle action potential;

Fig. 1B is a schematic model of a cardiac muscle cell in an electrical field;

Fig. 2 is a schematic diagram of a heart having segments controlled in accordance with embodiments of the present invention;

Fig. 3 is a schematic diagram of a segment of right atrial tissue with a plurality of conduction pathways, illustrating the use of fences, in accordance with a preferred embodiment of the present invention;

Fig. 4A is a schematic diagram of an electrical controller connected to a segment of cardiac muscle, in accordance with a preferred embodiment of the invention;

Fig. 4B is a schematic diagram of an electrical controller connected to a segment of cardiac muscle, in accordance with a preferred embodiment of the invention;

Fig. 5 is a schematic diagram of an experimental setup used for testing the feasibility of some embodiments of the present invention;

Figs. 6A-6C are graphs showing different experimental results;

Fig. 7A is a graph summarizing results of experimentation on an isolated segment of cardiac muscle fibers, and showing the effect of a delay in applying a pulse in accordance with an embodiment of the invention on the increase in contractile force;

Fig. 7B is a graph summarizing results of experimentation on an isolated segment of cardiac muscle fibers, and showing the effect of a polarity of the pulse on the increase in contractile force;

Fig. 7C is a graph summarizing results of experimentation on an isolated segment of cardiac muscle fibers, and showing the effect of a duration of the pulse on the increase in contractile force;

Fig. 7D is a graph summarizing results of experimentation on an isolated segment of cardiac muscle fibers, and showing the effect of a current intensity of the pulse on the increase in contractile force;

Fig. 8 is a series of graphs shows the repeatability of increasing contractility in various types of cardiac muscles;

Fig. 9 is a series of graphs showing experimental results from a first experiment in which an isolated rabbit heart was controlled in accordance with an embodiment of the present invention;

Fig. 10 is a series of graphs showing experimental results from a second experiment in which an isolated rabbit heart was controlled in accordance with an embodiment of the present invention;

Fig. 11 is a series of graphs showing experimental results from a third experiment, repeating the second experiment and its results;

Fig. 12 is a series of graphs showing experimental results from a fourth experiment, which was performed on the heart of the experiment of Fig. 11;

Fig. 13 is a series of graphs showing experimental results from a fifth experiment, showing an increase in aortic pressure;

Fig. 14 is a series of graphs showing experimental results from a sixth experiment, showing an increase in aortic flow and in aortic pressure; and

Fig. 15 is a series of graphs showing experimental results from a seventh experiment, showing an increase in aortic flow.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

One preferred embodiment of the present invention relates to increasing the contractility and/or the plateau duration in a segment of heart muscle by applying an electric field or current across the segment. As used herein, the terms, voltage, electric field and current are used interchangeably to refer to the act of supplying a non-excitatory pulse. The actual method of applying the pulse is described in more detail below.

Fig. 1B shows a model illustrating one possible explanation for the relation between an applied voltage and a resulting plateau duration. A cell 20, having a membrane 26 surrounded by extra-cellular fluid 28 is located in an electrical field generated by an electrode 22 and an electrode 24. Cell 20 has a -40 millivolts internal potential across membrane 26, electrode 22 has a potential of 40 millivolts and electrode 24 is grounded (to the rest of the body). During the plateau, calcium ions enter the cell and potassium ions leave the cell. In this model, the external electric field caused by the voltage on electrodes increases the potential of extra-cellular fluid 28. This reduces the outward movement of potassium ions from inside cell 20 and/or forces calcium ions into cell 20.

In an additional or alternative model, the electric field generated by electrodes 22 and 24 causes an ionic flow between them. This flow is carried mainly by calcium and potassium ions, since these are the ions to which membrane 26 is permeable. In this model, calcium ions are drawn into cell 20 by the current while potassium ions are removed. Alternatively or additionally, sodium ions are removed instead of potassium ions. In any case, the additional calcium ions in the cell increase the contractility of cell 20 and are believed to extend the plateau duration.

Another additional or alternative model is that the electric field and/or the ionic current affect the opening and closing of voltage-gated gates (sodium, potassium and sodium-calcium). Further, the field may affect the operation of ionic pumps. One possible mechanism for this effect is that the applied electric field generates local "hot spots" of high electrical fields in the cell membrane, which hot spots can affect the opening and closing of ionic channels and/or pumps. Since the cell is generally asymmetric with regard to the creation of these hot spots and since the channels themselves have an asymmetric behavior with respect to applied fields, more channels may be opened at one end of the cell than at the other. If, for example, more channels open at the negative end of the cell than at the positive end of the cell, the inflow of calcium ions will be greater than the outflow of these ions.

Different types of ionic channels and pumps have different operating characteristics. These characteristics include flowrates, opening and closing rates, triggering voltage levels, priming and dependency on other ions for operating. It is thus possible to select a particular type of ionic channel by applying a particular strength of electric field, which strength also depends on whether the channels are open or closed at that moment, i.e., on the depolarization/repolarization phase of the cell. Different attributes of cellular activity may be controlled by controlling the ionic

channels in this manner, since the activity of excitable tissues are well determined by their trans-membrane potential and the concentrations of various types of ions inside and outside the cell.

Another, "recruitment", model, hypothesizes that the non-excitatory pulse recruits cardiac muscle fibers which are otherwise not stimulated by the activation signal. The non-excitatory pulse may work by lowering their depolarization threshold or by supplying a higher strength activation signal than is normal.

Most probably, one or more of these models may be used to explain the activity of cell 20 during different parts of the activation cycle. However, several major effects, including, increasing contractility, changing the self-activation rate, rescheduling of the repolarization, extension of plateau duration, hyper-polarization of cells, membrane potential, changing of conduction velocity and inactivation of cells using electric fields, can be effected without knowing which model, if any, is correct.

As can be appreciated, the direction of the electric field may be important. First, conduction in cardiac cells is very anisotropic. Second, the distribution of local irregularities in the cell membrane is not equal, rather, irregularities are more common at ends of the cell; in addition, one cell end is usually more irregular than the other cell end. These irregularities may govern the creation of local high electric fields which might affect ionic channels. Third, there exist voltage potentials in the heart which are caused by the depolarization and repolarization of the heart itself and which may interfere with an externally applied electric field. In one preferred embodiment of the invention, the purpose of a particular electric field is to induce an ionic current which is opposite to an ionic current induced by the voltage potential caused by the rhythmic depolarization of the heart. For example, the plateau duration in cardiac muscle cells further from the earliest activation location is typically shorter than the duration of those cells nearer the earliest activation location. This shortening may result from ionic currents caused by the depolarization and repolarization of the heart. These ionic currents can be negated by applying an electric field of an equal magnitude and opposite direction to the field generated by the rhythmic depolarization.

Fig. 2 shows a heart 30 which is controlled using an electrical controller 32. A segment 38 of the right atrium is a controlled segment. In one preferred embodiment of the invention, the casing of controller 32 is one electrode and an electrode 36 is a second electrode for applying an electric field to segment 38. In another preferred embodiment of the invention, a second electrode 34 is used instead of the casing of controller 32. In a further preferred embodiment of the invention, the body of controller 32 is a ground, so that both electrode 34 and electrode 36 can be positive or negative relative to the rest of the heart. In another embodiment, electrode 34 is not directly connected to heart 30, rather, electrode 34 is floating inside the heart.

In an alternative embodiment, also shown in Fig. 2, the electric field is applied along the heart wall, rather than across it. A segment 35 of the left ventricle is shown to be controlled by

two electrodes 37 operated by a controller 39. Electrodes 37 may be placed on the surface of heart 30, alternatively, electrodes 37 may be inserted into the heart muscle.

It should be appreciated that a current induced between the electrodes may cause electrolytic deposition on the electrodes over a period of time and/or may cause adverse physiological reactions in the tissue. To counteract this effect, in a preferred embodiment of the invention, the electric field is an AC electric field. In one preferred embodiment, the direction of the field is switched at a relatively low frequency, equal to or lower than the cardiac cycle rate. Preferably, the phase is inverted during a particular phase of the cardiac cycle, for example, during diastole. In another preferred embodiment of the invention, the electric field has a frequency which is significantly higher than the cardiac cycle. As is well known, some of the ionic gates and pumps have an asymmetric activation profile, in that they open in response to a triggering event faster then they close in response to an inactivating event. In some cases, such as fast sodium channels, the triggering and inactivation events are local potentials. For example, the fast sodium gates require less than half a millisecond to open and up to about a millisecond to close. Thus, if the frequency of the field is high enough, certain pumps can be activated and gates kept open even though the average voltage is zero.

In accordance with another preferred embodiment of the invention, an AC field is overlaid on a DC field for controlling the heart. For example, an AC field having a amplitude of 20% that of the DC field and a frequency of 1Khz may be used. The AC field may be a sawtooth shape, a sinusoidal shape or in another form. Such an AC/DC controlling pulse has the advantage that the change in the applied field is higher, so that any reactions (on the part of the muscle cell) to the change in the field are facilitated, as well as any reaction to the intensity of the field.

Alternatively or additionally, various types of ionic electrodes, such as Ag-AgCl or platinum electrodes may be used.

There are two preferred methods of delivering an electric field to a segment of the heart. In a first method, a current is forced through the segment of the heart which is to be controlled. Preferably, the current is a constant DC current. However, an AC current, as described above may also be used. In a second method, an electric field is applied across the heart and maintained at a constant strength. Generally, applying an electric field is easier and requires less power than inducing a current.

The timing of the application of the electric field (or current) relative to the local activity at segment 38 and relative to the entire cardiac cycle is important. In general, the application of the field may be synchronized to the local activation time if a local effect is desired, such as increasing the local contractility and/or plateau duration. The application of the field may be synchronized to the cardiac cycle in cases where a global effect is desired. For example, by hyper-polarizing cells in synchrony with the cardiac cycle it is possible to time their excitability window such that certain arrhythmias are prevented, as described in greater detail below. The application of the field may also be synchronized in accordance with a model of how the heart should be

activated, in order to change the activation profile of the heart. For example, to increase the output of the heart, conduction velocities and/or conduction pathways may be controlled so that the heart contracts in a sequence deemed to be more optimal than a natural sequence. It should however be appreciated that the difference in activation times between different parts of the heart, especially in the same chamber of the heart, is usually quite small. For example, the propagation time of an activation signal in the left ventricle is approximately 15 milliseconds. If the control function may be achieved even if the timing of the application of the field is off by 5 or 10 milliseconds, then the control function can be achieved using a single pair of controlling electrodes.

If an electric field is applied before the activation signal reaches segment 38, the electric field can be used to reduce the sensitivity of segment 38 to the activation signal. One method to produce this effect is to apply a large electric field opposite to the direction of the activation signal and synchronized to it. This field will reduce the amplitude of the activation signal, so that it cannot excite cardiac tissue. Another method is to apply a strong positive potential on segment 38 before an activation signal reaches it, so that segment 38 is hyper-polarized and not sensitive to the activation signal. Removing the electric field does not immediately cancel this effect. Segment 38 stays insensitive for a short period of time and for a further period of time, the conduction velocity in segment 38 is reduced. In some cases however, removing the electric field will cause an action potential. This action potential can be timed so that it occurs in a safe period with regard to the activation profile of the heart, so that if the segment generates an activation signal, this signal will not be propagated to other part of the heart. Other applications of electric fields can increase the conduction velocity, especially where the conduction velocity is low as a result of tissue damage. Another method is to apply an electric field similar to that used for defibrillation. When applied during the repolarization period of these cells, this type of electric field delays the repolarization. During this delayed/extended depolarization the cells are non-excitable. It should be appreciated that if this "defibrillation field" is applied using the techniques described herein (small, local and synchronized to a local activation time) the heart itself will not be defibrillated by the electric field.

Fig. 3 illuminates one use of extending the refractory periods of cardiac tissue. Segment 40 is a portion of a right atrium. An activation signal normally propagates from an SA node 42 to an AV node 44. Several competing pathways, marked 46A-46D, may exist between SA node 42 and AV node 44, however, in healthy tissue, only one signal reaches AV node 44 within its excitability window. In diseased tissue, several signals which have traveled in different paths may serially excite AV node 44 even though they originated from the same action potential in the SA node. Further, in atrial fibrillation, the entire right atrium may have random signal running through it. In a preferred embodiment of the invention, electric fields are applied to a plurality of regions which act as "fences" 48A and 48B. These fences are non-conducting to activation signals during a particular, predetermined critical time, depending on the activation time of the

electric fields. Thus, the activation signal is fenced in between SA node 42 and AV node 44. It is known to perform a surgical procedure with a similar effect (the "maze" procedure), however, in the surgical procedure, many portions of the right atrium need to be ablated to produce permanent insulating regions (fences). In the present embodiment of the invention, at least portions of fences 48A and 48B may be deactivated after the activation signal has passed, so that the atrium can contract properly.

Still another preferred embodiment of the invention relates to treating ventricular fibrillation (VF). In VF, a ventricle is activated by more than one activation signal, which do not activate the ventricle in an orderly fashion. Rather, each segment of the ventricle is randomly activated asynchronously with the other segments of the ventricle and asynchronously with the cardiac cycle. As a result, no pumping action is achieved. In a preferred embodiment of the invention, a plurality of electrical fences are applied in the affected ventricle to damp the fibrillations. In general, by changing the window during which segments of the ventricle are sensitive to activation, a fibrillation causing activation signal can be blocked, without affecting the natural contraction of the ventricle. In one embodiment of the invention, the fences are used to channel activation signals along correct pathways, for example, only longitudinal pathways. Thus, activation signals cannot move in transverse direction and will quickly fade away, harmlessly. Healthy activation signals from the AV node will not be adversely affected by the fences. Alternatively or additionally, fences are generated in synchrony with the activation signal from the AV node, so that fibrillation causing activation signals are blocked. Further alternatively, entire segments of the ventricle are desensitized to the activation signals by applying a positive potential to those segments deemed sensitive to fibrillation.

Dividing the heart into insulated segments using fences is useful for treating many types of arrhythmia. By insulated, it is meant that conduction of the activation signal is blocked or slowed down or otherwise greatly reduced by deactivating portions of the heart conduction system. For example, many types of ventricular tachycardia (VT) and premature beats in the heart are caused by local segments of tissue which generate a pacing signal. These segments can be insulated from other segments of the heart so that only a small, local segment is affected by the irregular pacing. Alternatively, These diseased segments can be desensitized using an electric field, so that they do not generate incorrect activation signals at all.

Premature beats are usually caused by an oversensitive segment of the heart. By applying a local electric field to the segment, the sensitivity of the segment can be controlled and brought to similar levels as the rest of the heart, solving the major cause of premature beats.

It should be appreciated that it is not necessary to know the exact geometrical origin of an arrhythmia to treat it using the above described methods. Rather, entire segments of the heart can be desensitized in synchrony with the cardiac cycle so that they do not react before the true activation signal reaches them. Further, the heart can be divided into isolated segments or fenced in without mapping the electrical system of the heart. For example, electrodes can be inserted in

the coronary vessels to create fences in the heart. These fences can block most if not all of the irregular activation signals in the heart and still allow "correct" activation signals to propagate by synchronizing the generation of these fences to the "correct" cardiac activation profile.

In an additional preferred embodiment of the present invention, segments of the heart are continuously controlled using an electric field, so that their resting potential is below 60 millivolts. Below this level, the voltage-gated sodium gates cannot be opened by an activation signal. Thus, the reaction of the segments of the heart to an activation signal is reduced and has a longer delay. Other resting potentials may affect the opening of other voltage-gated gates in the cell.

Another preferred embodiment of the invention relates to cardiac surgery. In many instances it is desirable to stop the pumping action of the heart for a few seconds or minutes necessary to complete a suture or a cut or to operate on an aneurysm. Current practice is not very flexible. In one method, the heart is bypassed with a heart-lung machine and the heart itself is stopped for a long period of time. This process is not healthy for the patient as a whole or for the heart itself. In another method, the heart is cooled down to reduce its oxygen consumption and it is then stopped for a (non-extendible) period of a few minutes. The period is non-extendible in part since during the stoppage of the heart the entire body is deprived of oxygen.

Cession or reduction of the pumping activity of the heart may be achieved using methods described herein, for example, fencing. Thus, in a preferred embodiment of the invention, the pumping action of the heart (but not necessarily the electrical activity) is markedly reduced using techniques described herein, repeatedly, for short periods of time. It should be appreciated that due to the simplicity of application and easy reversibility, stopping the heart using electrical control is more flexible than currently practiced methods. Electrical control is especially useful in conjunction with endoscopic heart surgery and endoscopic bypass surgery, where it is desirable to reduce the motion of small segments of the heart.

Another preferred embodiment of the present invention relates to treating ischemic portions of the heart. Ischemic portions, which may be automatically identified from their injury currents using locally implanted sensors, may be desensitized to the activation signal of the heart. Thus, the ischemic cells are not required to perform work and may be able to heal.

U.S. provisional application titled "Cardiac Electromechanics", filed on January 10, 1996, by Shlomo Ben-Haim and Maier Fenster, and its corresponding Israeli patent application No. 116,699 titled "Cardiac Electromechanics", filed on January 8, 1996 by applicant Biosense Ltd., the disclosures of which are incorporated herein by reference describe methods of cardiac modeling and heart optimization. In cardiac modeling, the distribution of muscle mass in the heart is changed by changing the workload of segments of the heart or by changing the plateau duration at segments of the heart. These changes may be achieved by changing the activation profile of the heart. Plateau duration can be readily controlled using methods as described hereinabove. Further, by controlling the conduction pathways in the heart, according to methods

of the present invention, the entire activation profile of the heart can be affected. In cardiac optimization as described in the applications, the activation profile of the heart is changed so that global parameters of cardiac output are increased. Alternatively, local physiological values, such as stress, are redistributed to relieve high-stress locations in the heart. In a preferred embodiment of the present invention, the activation profile may be usefully changed using methods as described hereinabove.

In order to best implement many embodiments of the present invention, it is useful to first generate an electrical, geometrical or mechanical map of the heart. U.S. Patent Application No. 08/595,365 titled "Cardiac Electromechanics", filed on February 1, 1996, by Shlomo Ben-Haim, the disclosure of which is incorporated herein by reference describes maps and methods and means for generating such maps. U.S. Patent 5,391,199, U.S. Patent application No. 08/293,859, filed on August 19, 1994, titled "Means and Method for Remote Object Position and Orientation Detection System" and PCT US95/01103, now published as WO96/05768 on February 29, 1996, the disclosures of which are incorporated herein by reference, describe position sensing means suitable for mounting on a catheter which are especially useful for generating such maps. Such position sensing means may also be useful for correctly placing electrodes in the heart.

In one preferred embodiment of the invention, a map of the heart is used to determine which portions of the heart are viable, and thus, can be controlled to increase the cardiac output. Preferably, the entire activation profile of the heart is taken into account when determining to which portions of the heart a controlling field should be applied to maximize a parameter of cardiac output. The activation profile may also determine the timing of the application of the field. A perfusion map may be used to asses the blood flow to various portions of the heart. It is to be expected that increasing the contractility of a segment of heart muscle also increases the oxygen demand of that segment. Therefore, it is desirable to increase the contractility only of those segments which have a sufficient blood flow. Possibly, the oxygen demands of other segments of the heart is reduced by proper controlling thereof. Alternatively or additionally to mapping the perfusion and/or viability of the heart, the onset of controlling the heart may be performed gradually. Thus, the cardiac blood supply has time to adapt to the increased demand. In addition, the increase in demand will not be acute, so no acute problems (such as a heart attack) are to be expected as a result of the controlling. In one embodiment, the controlling is applied, at first, only every few heart beats, and later, every heart beat. Additionally or alternatively, the duration of a controlling pulse is gradually increased over a long period of time. Additionally or alternatively, different segments are controlled each heart beat, to spread the increased demand over a larger portion of the heart.

One benefit of many embodiments of the present invention, is that they can be implemented without making any structural or otherwise permanent changes in the conduction system of the heart. Further, many embodiments may be used in conjunction with an existing pacemaker or in conjunction with drug therapy which affects the electrical conduction in the

heart. In addition, different controlling schemes may be simultaneously practiced together, for example, controlling the heart rate and increasing contractility in the left ventricle.

It must be appreciated however, that by changing the activation profile of the heart, some changes may be effected on the structure of the heart. For example, cardiac modeling, as described above, may result from the activation profile changes, over time.

Fig. 4A is a schematic diagram of an electrical controller 50 in accordance with a preferred embodiment of the invention. A muscle segment 56, which is controlled by controller 50 is preferably electrified by at least one electrode 52 and preferably a second electrode 54. A sensor 58 may be used to determine the local activation time of segment 56, as an input to the controller, such as for timing the electrification of the electrodes. Other additional or alternative local and/or global cardiac parameters may also be used for determining the electrification of the electrodes. For example, the electrode(s) may be used to sense the local electrical activity, as well known in the art. Alternatively, sensor 58 is located near the SA node for determining the start of the cardiac rhythm. Alternatively, sensor 58 is used to sense the mechanical activity of segment 56, of other segments of the heart or for sensing the cardiac output. In one embodiment, sensor 58 senses the electrical state of the heart, controller 50 determines a state of fibrillation and electrifies electrodes 52 and 54 accordingly.

Fig. 4B shows an alternative embodiment of the invention, where a heart segment 55 is controlled by a plurality of electrodes 57 which are connected to a controller 59. The use of many electrodes enables greater control of both spatial and temporal characteristics of the applied electric field. In one example, each one of electrodes 55 is used to determine its local activation time. Controller 59 individually electrifies electrodes 55 according to the determined activation time.

Different embodiments of the present invention will typically require different placement of the control electrodes. For example, some embodiments require a large area electrode, for applying an electric field to a large portion of the heart. In this case, a net type electrode may be suitable. Alternatively, a large flat electrode may be placed against the outside of the heart. Other embodiments require long electrodes, for example, for generating fences. In this case, wires are preferably implanted in the heart in parallel to the wall of the heart, optionally, they may be placed in the coronary vessels outside the heart.

In one embodiment of the invention, a pacemaker is provided which increases the output of a heart. A pacemaker activation pulse usually is a single pulse of a given duration, about 2 milliseconds in an internal pacemaker and about 40 milliseconds in an external pacemaker. In accordance with a preferred embodiment of the invention, a pacemaker generates a double pulse to excite a heart. A first portion of the pulse may be a stimulation pulse as known in the art, for example, 2 milliamperes constant current for 2 milliseconds. A second portion of the pulse is a pulse as described herein, for example, several tens of milliseconds long and at a short delay after the first portion of the pulse. Alternatively, a very long stimulation pulse may be used. This type

of pacemaker preferably uses two unipolar electrodes, one at the apex of the heart and one at the top of the left ventricle (or the right ventricle if it is right ventricular activity that is to be increased).

In a preferred embodiment of the invention, the pacemaker adapts to the physiological state of the body in which it is installed by changing the heart's activity responsive to the physiological state. The pacemaker can sense the state of the body using one or more of a variety of physiological sensors which are known in the art, including, pH sensors, pO sensors, pCO2 sensors, cardiac blood-flow sensors, acceleration sensors and pressure sensors. For example, the pacemaker can increase the flow from the heart in response to an increase in pCO2. Since these control is usually applied in a discrete manner over a series of cardiac cycles, this control may be termed a control sequence. The modification in the heart's activity may be applied gradually or, preferably, in accordance with a predetermined control sequence.

In one aspect of the invention, target values are set for at least one of the measured physiological variables and the pacemaker monitors these variables and the effect of the control sequence applied by the pacemaker to determine a future control sequence. Once the discrepancy between the target value and the measured value is low enough, the control sequence may be terminated. As can be appreciated, one advantage of a cardiac controller over a pacemaker is that it can control many aspect of the heart's activation profile. As a result, the controller can determine a proper tradeoff between several different aspects of the activation profile of the heart, including, heart output, oxygenation of the cardiac muscle, contractile force of the heart and heart rate.

Another aspect of the invention relates to modifying the relation between the contraction of the left ventricle and the contraction of the right ventricle. In a healthy heart, increased contraction of the left ventricle causes an increase in the input to the right ventricle, which in turn causes the right ventricle to pump harder. Decreased left ventricular output reduces the right ventricular output in the same manner. Some times it may be desirable to modify the flow from one ventricle without a corresponding change in the flow from the other ventricle. This may be achieved by simultaneously controlling both ventricles, one control increasing the flow from one ventricle while the other control decreases the flow from the other ventricle. This modification will usually be practiced for short periods of time only, since the vascular system is a closed system.

Another aspect of the present invention relates to performing a complete suite of therapies using a single device. A controller in accordance with a preferred embodiment of the invention includes several therapies which it can apply to the heart, including for example, increasing contractility, defibrillation, fencing heart rate control and pacing. The controller senses (using physiological sensors) the state of the body and decides on an appropriate short-term therapy, for example, defibrillation to overcome fibrillation, increasing the heart rate to increase the cardiac outflow or applying fences to restrain a sudden arrhythmia. Additionally or

alternatively, such a controller can change the applied control sequence in response to long term therapeutic goals. For example, if increasing contractility is used to increase the muscle mass in a portion of the heart, once a required muscle mass is reached, the control sequence may be stopped. This is an example of a therapeutic treatment affected by the controller. In another example, a few weeks after the device is implanted and programmed to increase the cardiac output to a certain target variable, the target variable may be changed. Such a change may be mandated by an expected period of time over which the heart adapts to the controller. One such adaptation is that the heart becomes stronger. Another such adaptation may be that the heart reduces its response to the control sequence, so that a different control sequence may be required to achieve the same goals.

In an alternative embodiment of the invention, a control device includes a human operator in the loop, at least during a first stage where the controller must "learn" the distinctive aspects of a particular heart/patient. At a later stage, the operator may monitor the therapeutic effect of the controller on a periodic basis and change the programming of the controller if the therapeutic effect is not what the operator desires.

In an additional embodiment of the invention, the controller is not implanted in the body. Preferably, the control sequence is applied using one or more catheter which are inserted into the vascular system. Alternatively, electrodes may be inserted directly through the chest wall to the heart.

Fig. 5 shows an experimental setup designed and used to test some embodiments of the present invention. A papillary muscle 60, from a guinea pig, was connected between a support 62 and a pressure transducer 64. Muscle 60 was stimulated by a pair of electrodes 66 which were connected to a pulsed constant current source 70. A pulse generator 74 generated constant current pacing pulses for electrodes 66. A pair of electrodes 68 were used to apply an electric field to muscle 60. A slave pulse generator 76, which bases its timing on pulse generator 74, electrified electrodes 68 via a pulsed constant current source 72. The force applied by the muscle was measured by transducer 64, amplified by an amplifier 78 and drawn on a plotter 80. Pulse generator 74 selectably generated activation pulses 500, 750, 1000 and 1500 milliseconds (t1) apart for variable activation of muscle 60. Pulse generator 76 generated a square wave pulse which started t2 seconds after the activation pulse, was t3 seconds long and had a selected current (in milliamperes) higher than zero.

Fig. 6A-6C are graphs showing some results of the experiments. In general, the results shown are graphs of the force of the muscle contractions after muscle 60 reaches a steady state of pulsed contractions. Fig. 6A is a graph of the results under the following conditions:

t1 (pacemaker pulse) = 750 milliseconds;

t2 (delay) = 150 milliseconds;

t3 (pulse duration) = 100 milliseconds; and

current= 100 milliamperes.

As can be seen, the force exerted by the muscle was increased by a factor of 2.5 when the controlling pulse (electrodes 68) was used as opposed to when electrodes 68 were not activated.

Fig. 6B is a graph of the force of muscle contractions under the following conditions:

t1= 1000 milliseconds;

t2= 20 milliseconds;

t3= 300 milliseconds; and

current= 75 milliamperes.

As can be seen, the amplitude of the contractions is extremely attenuated. When the polarity of the controlling signal was inverted after a few contractions, the contractions of muscle 60 were almost completely attenuated.

Fig. 6C is a graph of the force of muscle contractions under the following conditions:

t1= 1000 milliseconds;

t2= 20 milliseconds;

t3= 300 milliseconds; and

current= 10 milliamperes.

In this case, the effects of increasing the contractile force of muscle 60 remained for about two minutes after the electrification of electrodes 68 was stopped. Thus, the contraction of muscle 60 is dependent not only on the instantaneous stimulation and control but also on prior stimulation and control. The extended effect of this electrification setup may be a result of the high current intensity, which might have overwhelmed the muscle cells.

Using a similar experimental setup, additional experiments were performed, some on papillary muscles and some on cardiac muscles from the ventricles and atria walls. In these experiments, the test animal was usually a rabbit, however, in one case a rat was used. Most of these experiments used a DC constant current source which was in contact with the muscle, however, an electrical field scheme was also tested, and yielded similar results. In the electric field scheme, the electrodes were placed in the solution surrounding the muscle segment and not in contact with the muscle segment. The current used was 2-10 milliamperes. In a few experiments, no increase in contractile force was induced, however, this may be the result of problems with the electrodes (interaction with body fluids) and/or the current source. In general, many cycles of increases in contractility and return to a base line were performed in each experiment. In addition, the increases in contractility were repeatable in subsequent experiments. These increases were obtained over a pacing range of 0.5-3 Hz.

Figs. 7A-7D summarize the results obtained in these further experiments. It should be appreciated, that the time scales of the applied pulse are strongly associated with the pacing rate and with the animal species on which the experiment was performed. In these experiments, the pacing rate was usually about 1Hz. Within the range of .5-3Hz the pulse form required for an increase in contraction force is not substantially affected by the pacing rate. The intensities of the currents used in the experiments are affected by the electrode types used, and possibly by the

animal species, so that if other electrode types are used, different current intensities may be required for the same effect.

Fig. 7A shows the effect of a delay in the onset of the applied current on the increase in contractile force. A small delay, does not substantially affect the increase in contractile force.

Fig. 7B shows the effect of the polarity of the pulse on the increase in contractile force. Usually, one polarity generated a greater increase in contractile force than the opposite polarity.

In some experiments, reversing the polarity during an experiment actually decreased the contractile force, for a short while or for the entire duration of the pulse.

Fig. 7C shows the effect of pulse duration on the increase in contractile force. A very short pulse, on the order of 1 milliseconds does not substantially affect the contractile force. After about 20 milliseconds pulse duration, the increase in contractile force with increase in pulse duration is reduced, until at about 100 milliseconds duration there is no apparent further increase in contractile force.

Fig. 7D shows the effect of the current intensity on the increase in contractile force. It should be noted that above about 8 milliamperes the contractile force actually decreases below the baseline condition (where no current was applied). It may be that this effect is related to the above described theory of intra-cellular calcium stores, and that too much calcium in the cardiac muscle cell reduces the availability of these stores, and therefore, the cell's contractility.

In addition to the above summarized results, several experimental results deserve special notice.

In one experiment, a segment of a right atrium from a rabbit was allowed to set its own, intrinsic, pace (~2-3Hz). A non-excitatory current which was a constant current of between 0.2 and 2 milliamperes was driven through the tissue, for a duration of 100ms, the self pacing rate of the segment increased, as did the contractility (after a first, short, reduction in force).

In a second experiment, a right rabbit papillary muscle was paced at 1.5 Hz. The applied field was a constant current of between 2 and 4 milliamperes, in a pulse 70 ms long and no delay after the pacemaker pulse. The contractility increased by between 45% and 133%. The increased contractility was sustained at 3ma for as long as two hours. Stopping the applied field caused a rapid return to the original contractile force. Re-application of the field repeated the previous results.

In a third experiment, increasing the pulse duration of a 2ma current over the range 10 to 100 milliseconds in a left rabbit papillary muscle increased the contractile force, however, no effect on the duration of the muscle twitch was observed.

Fig. 8 is a series of graphs which shows an increase in contractility in several different muscle types (the horizontal bar indicates the application of a controlling electric field).

In another series of experiments, a whole living heart was removed from a rabbit (1-2 Kg in weight) and controlled using methods as described hereinabove. The apparatus for keeping the heart alive was an Isolated Heart, size 5, type 833, manufactured by Hugo Sachs Elektronik,

Gruenstrasse 1, D-79232, March-Hugstetten, Germany. In this apparatus, only the left ventricle is functional. The Pulmonary veins are connected to a supply hose, in which supply hose there is a warm (~37 °C) isotonic, pH balanced and oxygenated solution. The solution is pumped by the heart into the aorta. The heart itself is supplied with oxygen from the aorta, through the coronary arteries. The coronary veins empty into the right ventricle, from which the solution drips out. The solution which drips out (coronary blood flow) can be measured by collecting it in a measuring cup. Both the preload and the afterload of the vascular system can be simulated and preset to any desirable value. In addition, the total (heart+body) afterload and preload can be measured using this apparatus. In addition, the heart was connected to an ECG monitor, a pacemaker and a programmable pulse generator. The intra-cardiac pressure was measured using a pressure probe inserted into the ventricle. The flow through the aorta was measured using an electro-magnetic flowmeter. Various parameters, such as pH, pO2, pCO2 and temperature may be measured by attaching additional measurement devices. All the measurement devices may be connected to a computer which collects, and preferably analyzes the results.

A most noticeable experimental result was an increase in flow from the heart as a result of such a pulse. Another notable result was an increase in afterload as a result of such a pulse. Still another notable result was an increase in the developed left ventricular pressure, in the heart, when a non-excitatory pulse was applied.

Fig. 9 is a series of graphs showing the results of an experiment in which a 1.5 milliamperes constant current pulse, having a duration of 80 milliseconds and delayed 5 milliseconds after the pacing of the heart was applied. Two wire electrodes were used to apply this pulse, one electrode was placed at the apex of the heart (actually, overlaying the right ventricle) and one electrode was placed at the top of the left ventricle. The pacing was performed using a bipolar electrode, also placed near the apex of the heart. The pacing rate was approximately 10% higher than the normal pace. The pacing pulse was 2 milliseconds long, 2 milliamperes and at ~3.5Hz. In the experiments of Figs. 14-15, the pulse-electrodes were attached to the top and bottom of the left ventricle, respectively.

In Fig. 9, the application of the pulse can be seen as an increase in the magnitude of the ECG signal, since the pulse was not filtered from the ECG signal. In this experiment, an increase in the afterload (the actual pressure developing in the Aorta) and an increase in flow are clearly shown in Fig. 9. There is also an approximately 5% increase in LVP (Left ventricle pressure).

Fig. 10 is a series of graphs showing the results of an experiment in which a 2 milliamperes constant current pulse, having a duration of 80 milliseconds and delayed 5 milliseconds after the pacing of the heart. The wiring and pacing in this experiment were similar to the experiment described with reference to Fig. 9.

In Fig. 10, as in Fig. 9, a noticeable increase in afterload and flow can be ascertained from the graphs. In addition, a 5.6% increase in LVP was measured after applying the pulse.

Figs. 11 and 12 are series of graphs showing the results of an experiment which repeated the experiment of Fig. 10. Fig. 12 includes results from a latter time than Fig. 11, in the same heart. The increase in LVP and flow as a function of the application of the pulse is clear from the Figs. In addition, an immediate return to baseline (pre-pulse) values is also shown in these Figs.

Fig. 13 is a series of graphs showing experimental results from a fifth experiment, showing an average increase of 12% in aortic pressure. The pulse parameters were 6 milliamperes, 70 milliseconds duration and 5 milliseconds delay from the pacemaker pulse. Application of the pulse is indicated by the thickening of the ECG trace.

Fig. 14 is a series of graphs showing experimental results from a sixth experiment, showing an increase in aortic flow of about 27% and an increase in aortic pressure. The increase in flow is very important since one of the main problems with patients with congestive heart failure is a low cardiac flow. The pulse parameters were 5 milliamperes, 70 millisecond duration and 5 millisecond delay. Application of the pulse is indicated by the empty horizontal rectangles.

Fig. 15 is a series of graphs showing experimental results from a fifth experiment, showing an increase in aortic flow of about 20%. The pulse parameters were 5 milliamperes, 70 milliseconds duration and 5 milliseconds delay. Application of the pulse is indicated by the thick horizontal rectangle.

One interesting result of the isolated heart experiments relates to pulse forms which do not induce fibrillation in the heart. It was determined that the pulse should not extend more than about half the duration of the pressure wave (in this experimental setup, the pressure wave is measured, not electrical activity). In addition, a small delay (~5ms) between the pacing and the pulse also appears to protect against fibrillation.

Although the present invention has be described mainly with reference to the heart, it should be appreciated that preferred embodiments of the present invention may be applied to other types of excitable tissue. In one example, skeletal muscle and smooth muscle can be controlled as described hereinabove. It should however be appreciated, that most muscles have different ion gates and different resting potentials than cardiac muscle, so that the general principles must be adapted to the individual physiology. Further, the present invention may be applied to neural tissue. For example, epileptic fits and tetanization may be controlled by damping the excitability of neural tissue, as described above. Alternatively, electrical control may be used in conjunction with electrical stimulation of denervated or atrophied muscles to increase the precision of stimulation.

In a preferred embodiment of the invention, epileptic fits are controlled by suppressing Golgi cells, thus, reducing the excitability of associated neural tissues by reducing the amount of available calcium.

It will be appreciated by a person skilled in the art that the present invention is not limited by what has thus far been particularly described. Rather, the present invention is limited only by the claims which follow.

CLAIMS

1. A method of controlling a segment of cardiac muscle, comprising:

(a) sensing an activation time of said segment; and

(b) applying a non-exciting electric field to the segment at a time delay t1 after the activation time, for a duration of time t2.

2. A method of controlling a segment of cardiac muscle, comprising:

(a) providing at least one electrode near the muscle segment; and

(b) electrifying the at least one electrode to apply non-exciting electric fields to the muscle segment.

3. A method of controlling a segment of excitable tissue, comprising:

applying an electric field to the segment, wherein the electric field does not create an action potential in the tissue and wherein the electric field modifies at least one activation characteristic of the excitable tissue; and

repeating the application of said field after an activation signal reaches said tissue segment.

4. A method in accordance with claim 3, wherein the characteristic is a contraction force.

5. A method in accordance with claim 3, wherein the characteristic is a repolarization duration.

6. A method in accordance with claim 3, wherein the characteristic is an excitability of the tissue.

7. A method in accordance with any of the preceding claims, wherein said field is applied by applying an electric current to the tissue.

8. A method in accordance with any of the preceding claims, wherein the tissue is a heart.

9. A method in accordance with claim 8, wherein application of said electric field is gated to an activation signal of the heart.

10. A method in accordance with claim 8 or 9, wherein application of said field increases a flow output of the heart.

11. A method in accordance with any of claims 8-10, comprising, determining a local activation time of said segment relative to the cardiac cycle of the heart; and synchronizing the application of the field to the local activation time.

12. A method in accordance with any of claim 8-11, wherein said electric field changes the heart rate of the heart.

13. A pacemaker which performs the method of any of claims 1-12.

For the applicant,

Paul Fenster

Sanford T. Colb & Co.
c:25905

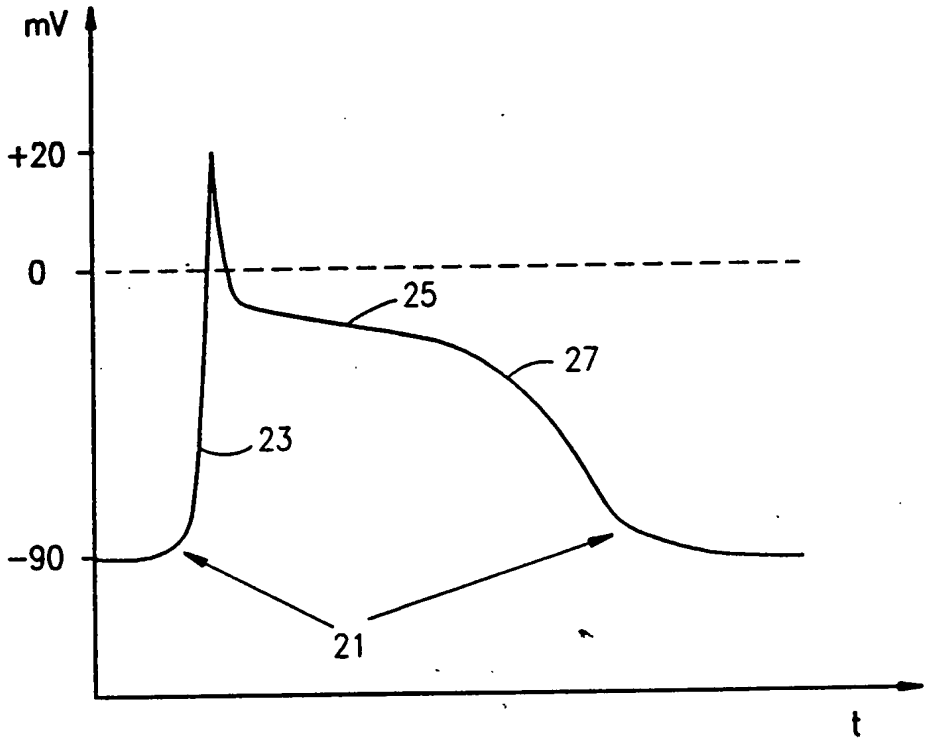


FIG. 1A

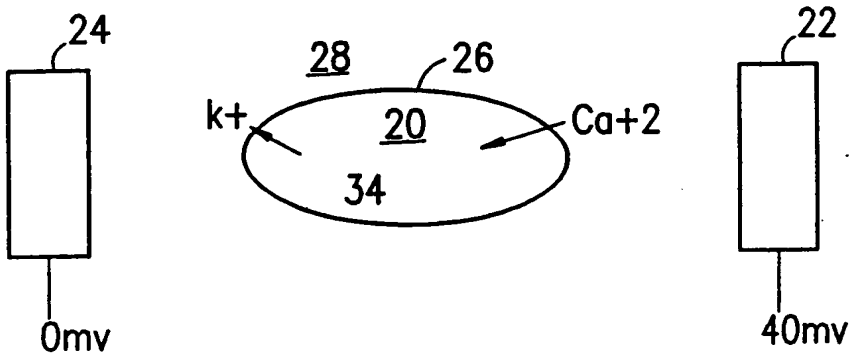


FIG. 1B

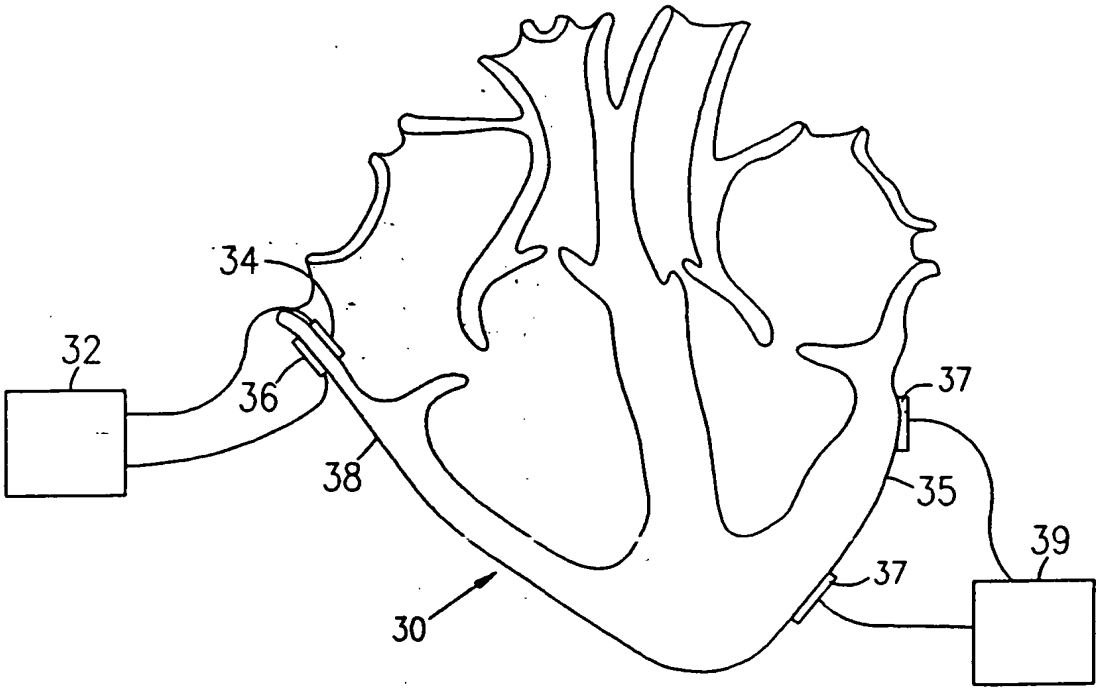


FIG. 2

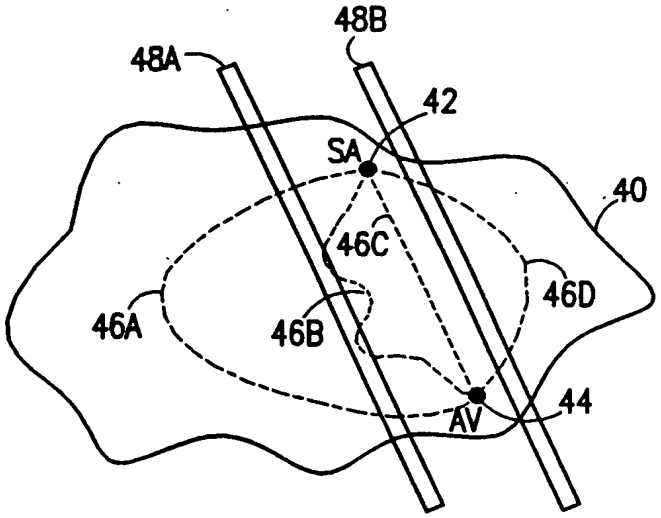


FIG. 3

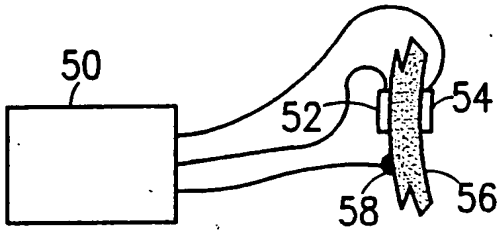


FIG. 4A

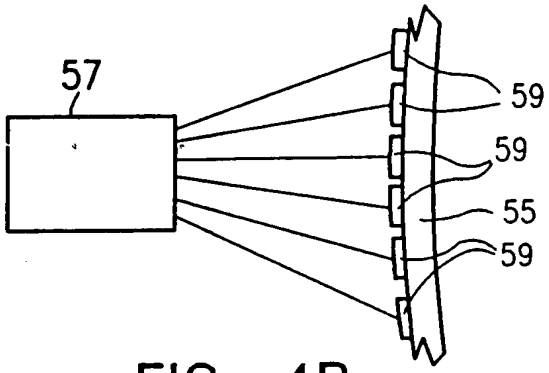


FIG. 4B

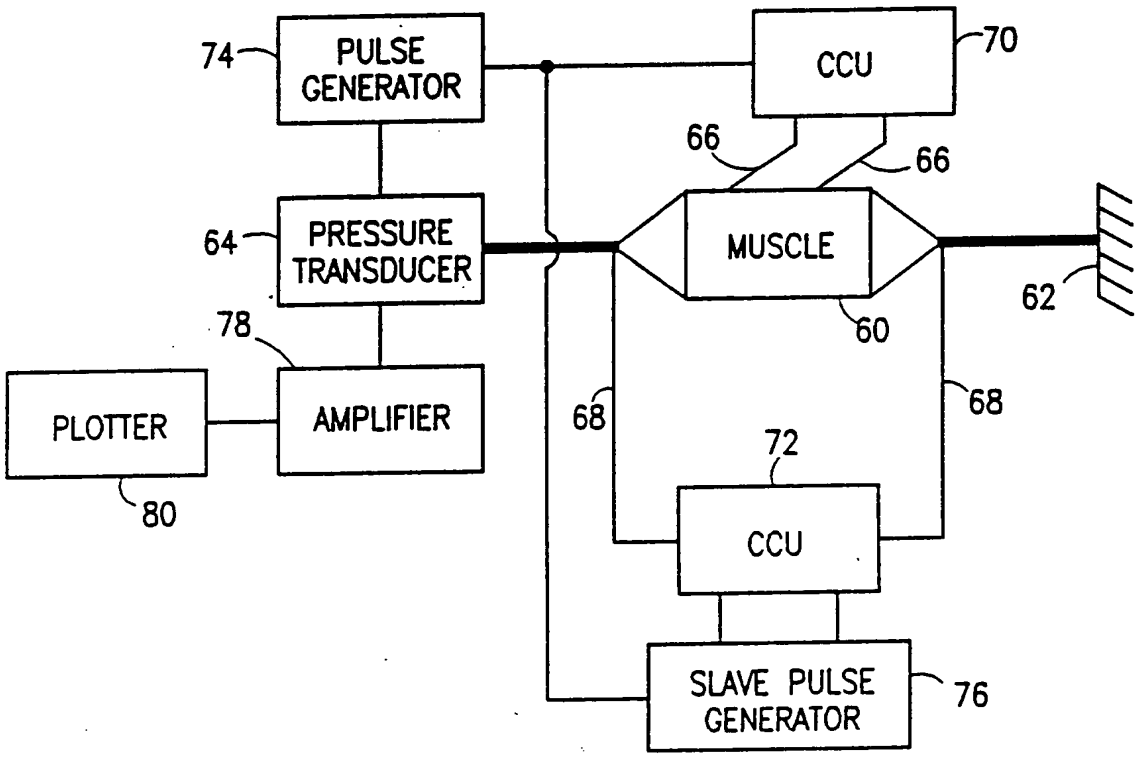

74
PULSE GENERATOR
CCU
70
66
66
64
PRESSURE TRANSDUCER
MUSCLE
62
60
78
PLOTTER
AMPLIFIER
68
68
72
CCU
SLAVE PULSE GENERATOR
76
80

FIG. 5

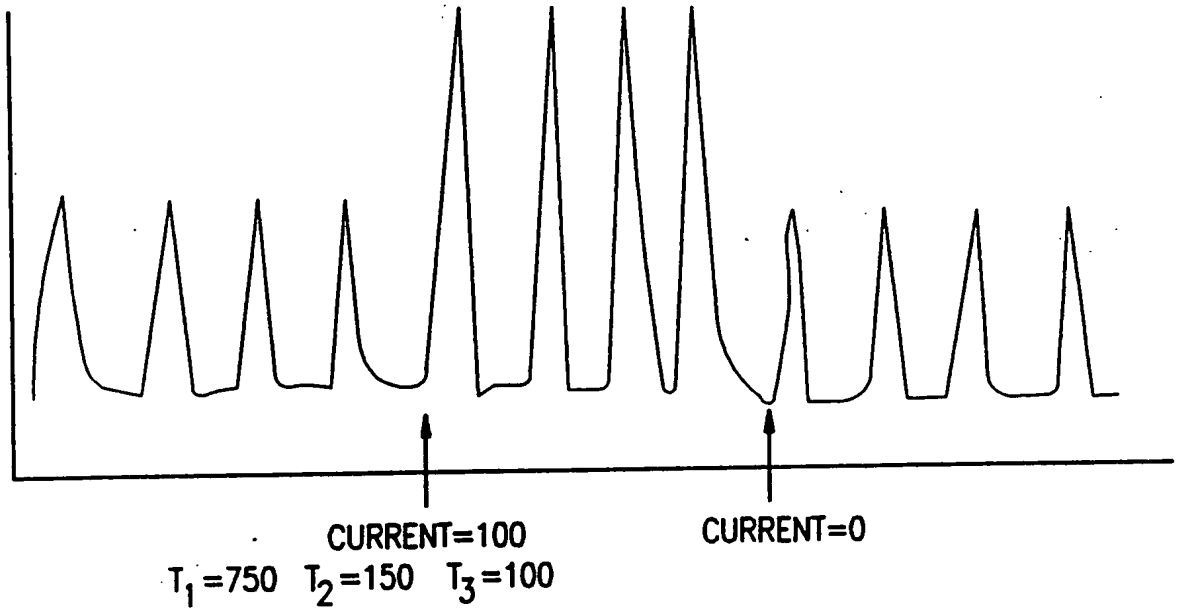

CURRENT=100
CURRENT=0
T_1=750 T_2=150 T_3=100

FIG. 6A

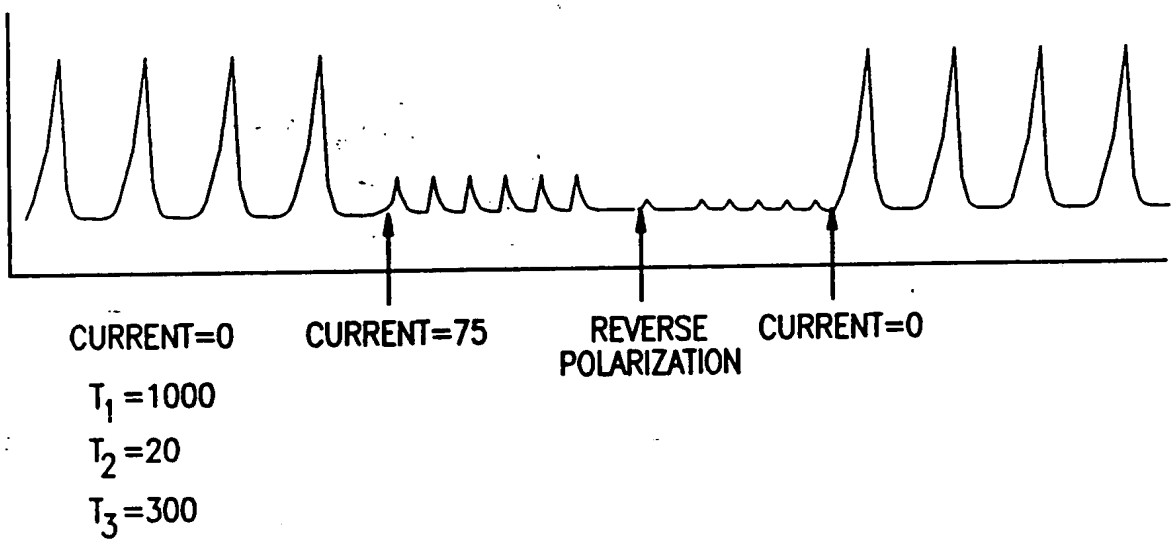

CURRENT=0
CURRENT=75
REVERSE POLARIZATION
CURRENT=0
T_1=1000
T_2=20
T_3=300

FIG. 6B

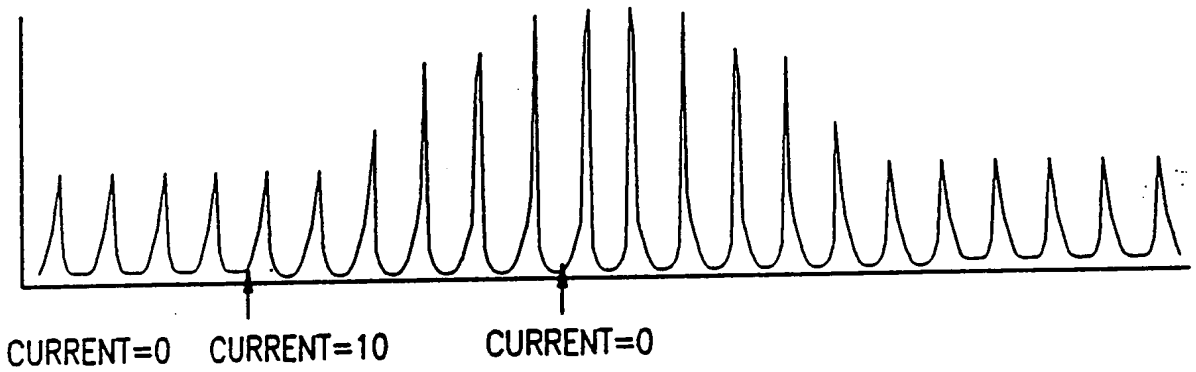


FIG. 6C

FIG. 7A

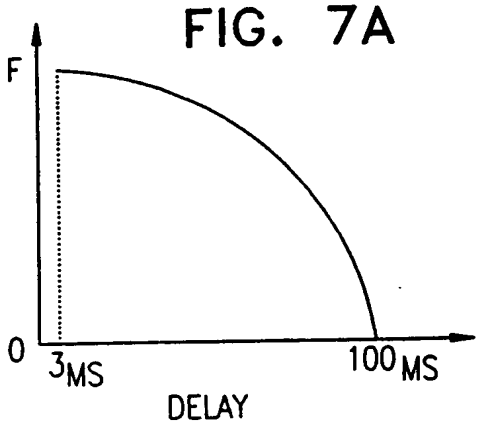


FIG. 7B

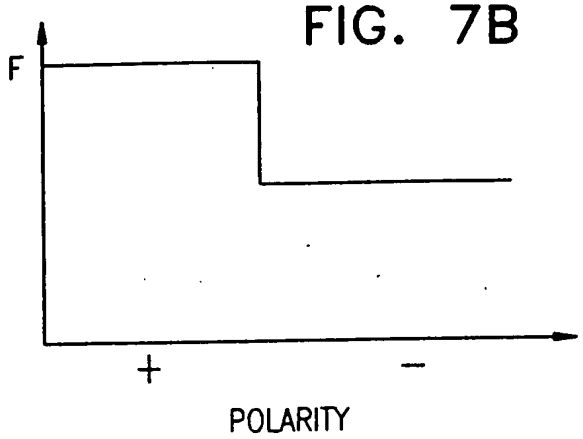


FIG. 7C

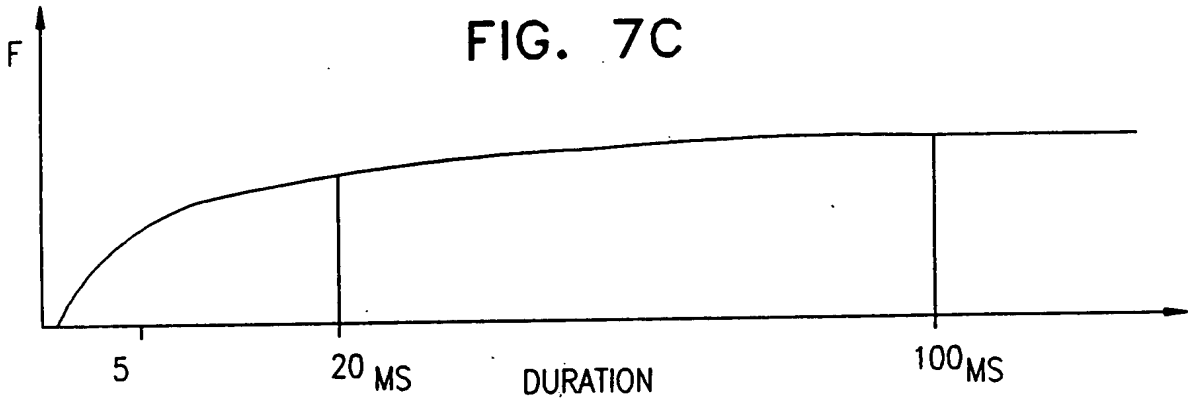
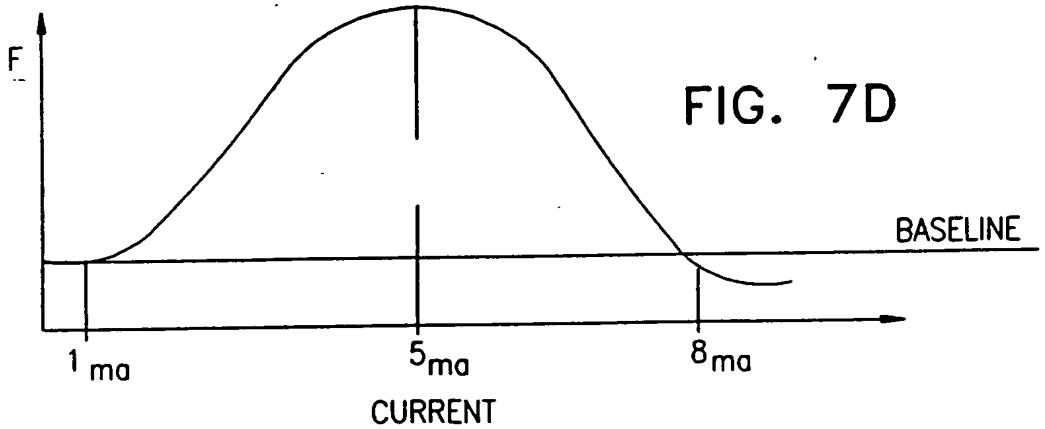
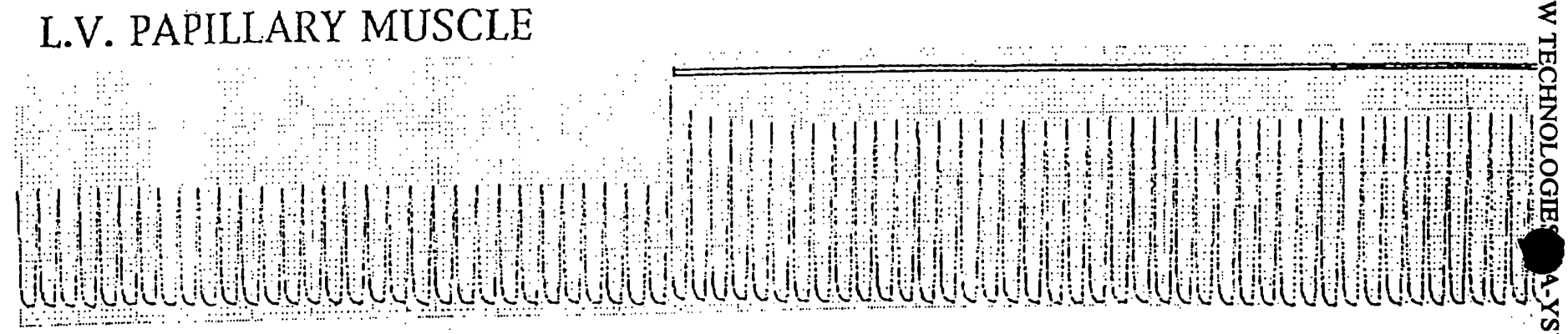


FIG. 7D





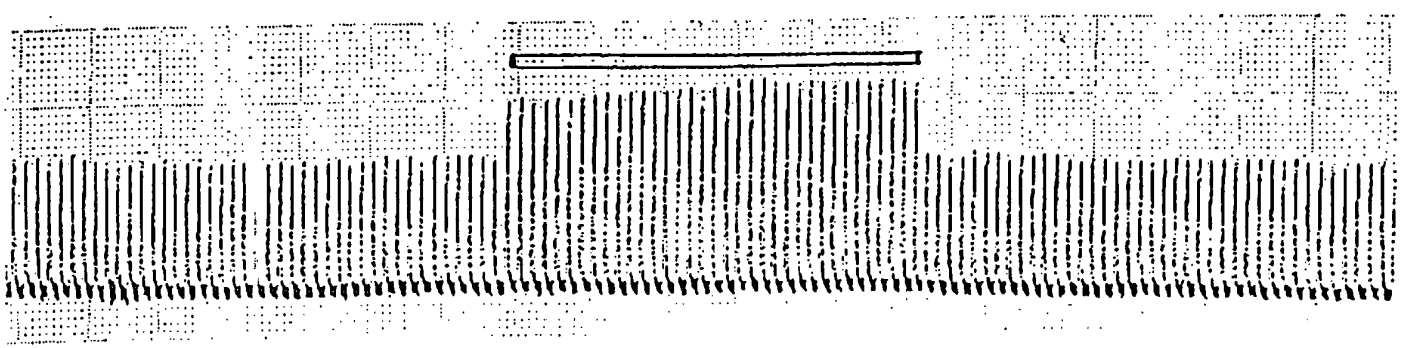
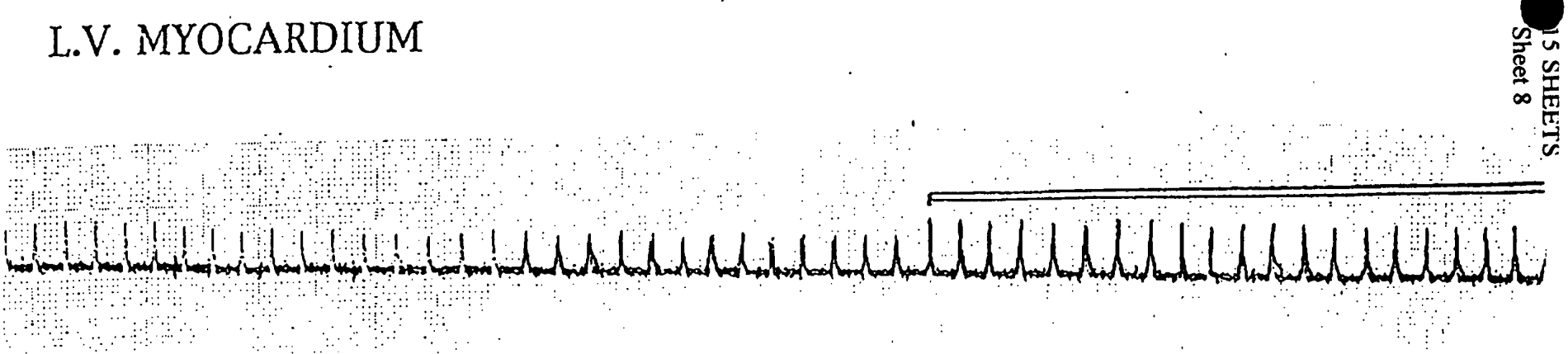


Fig. 8



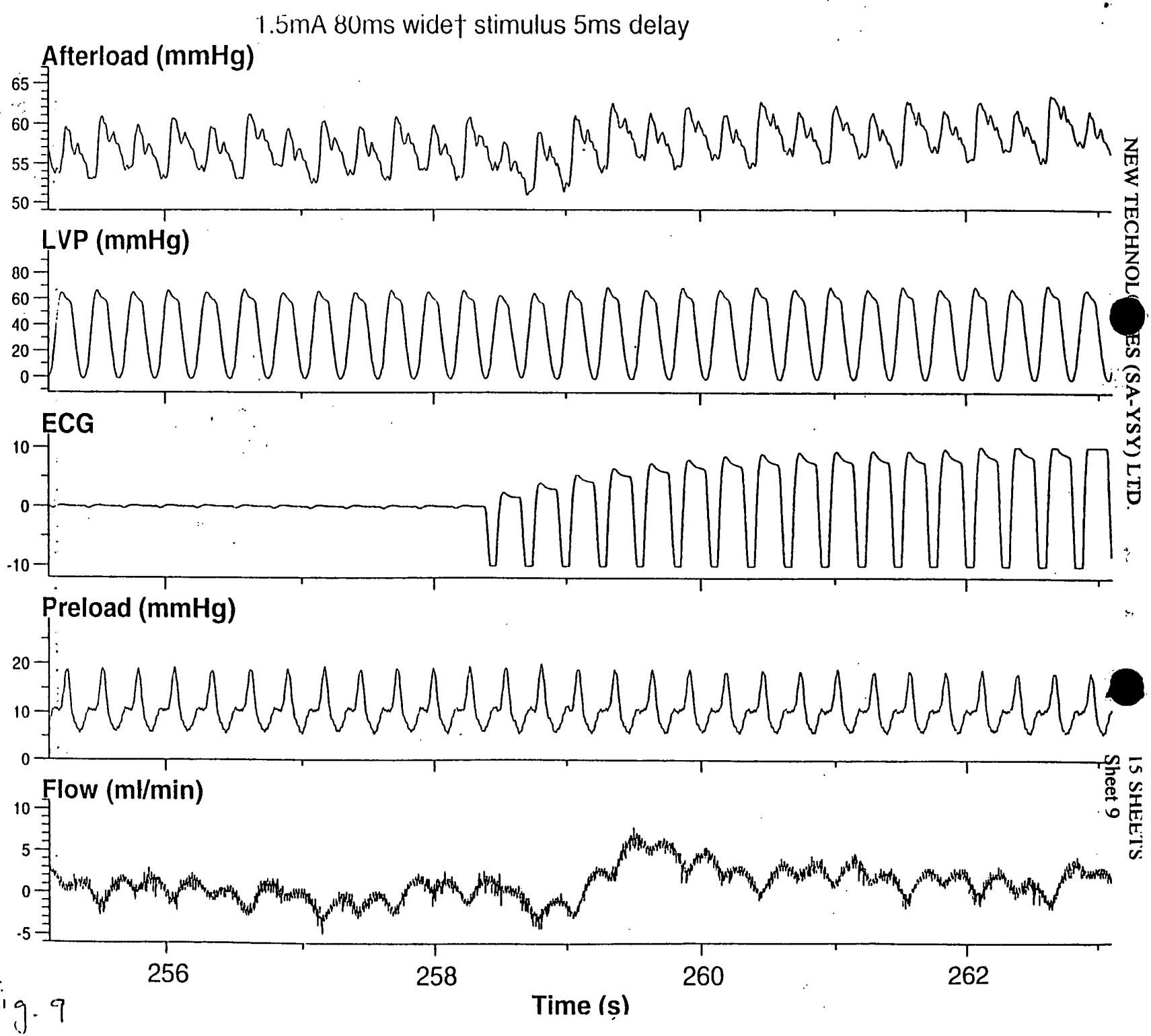


Fig. 9

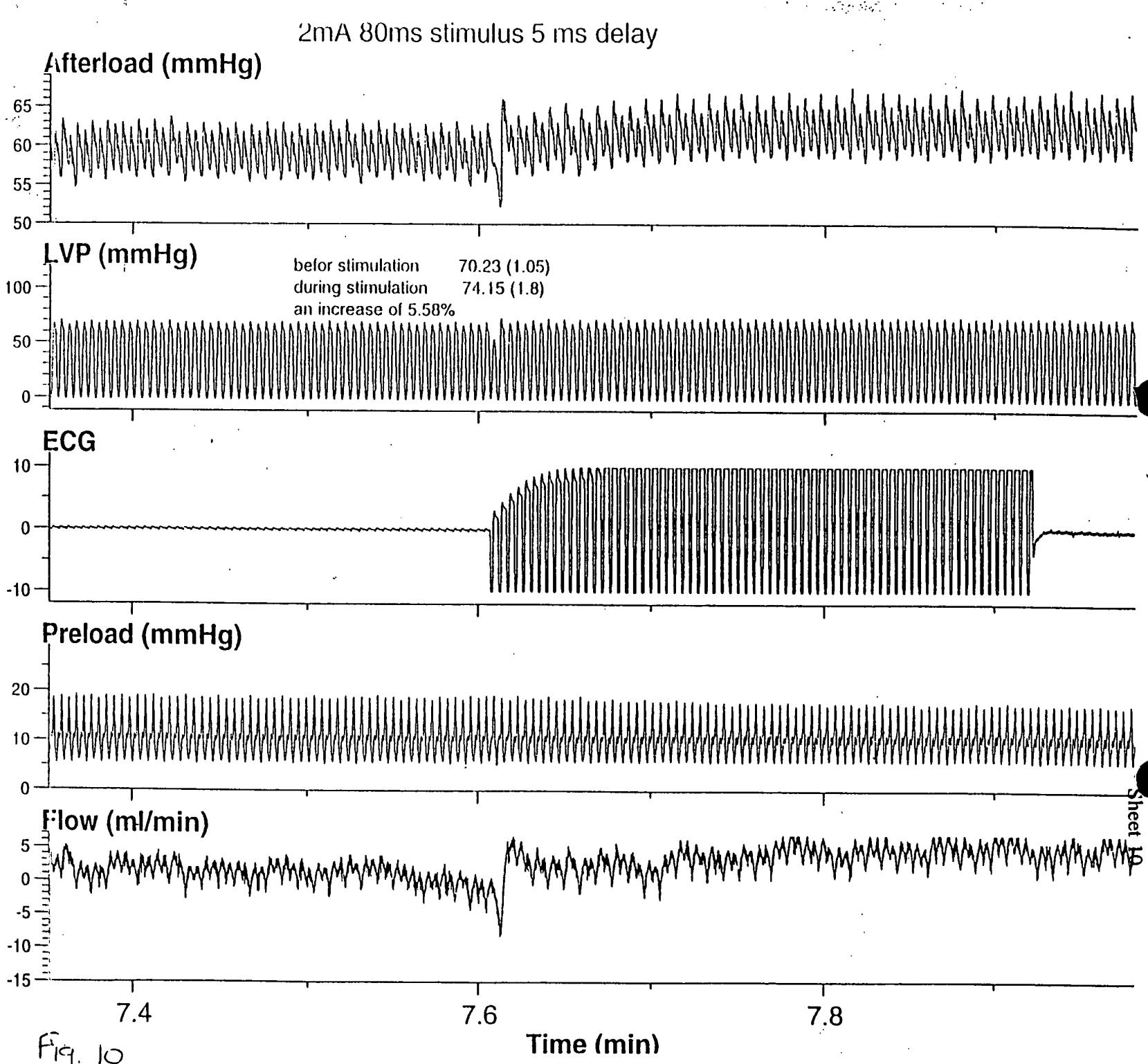


Fig. 10

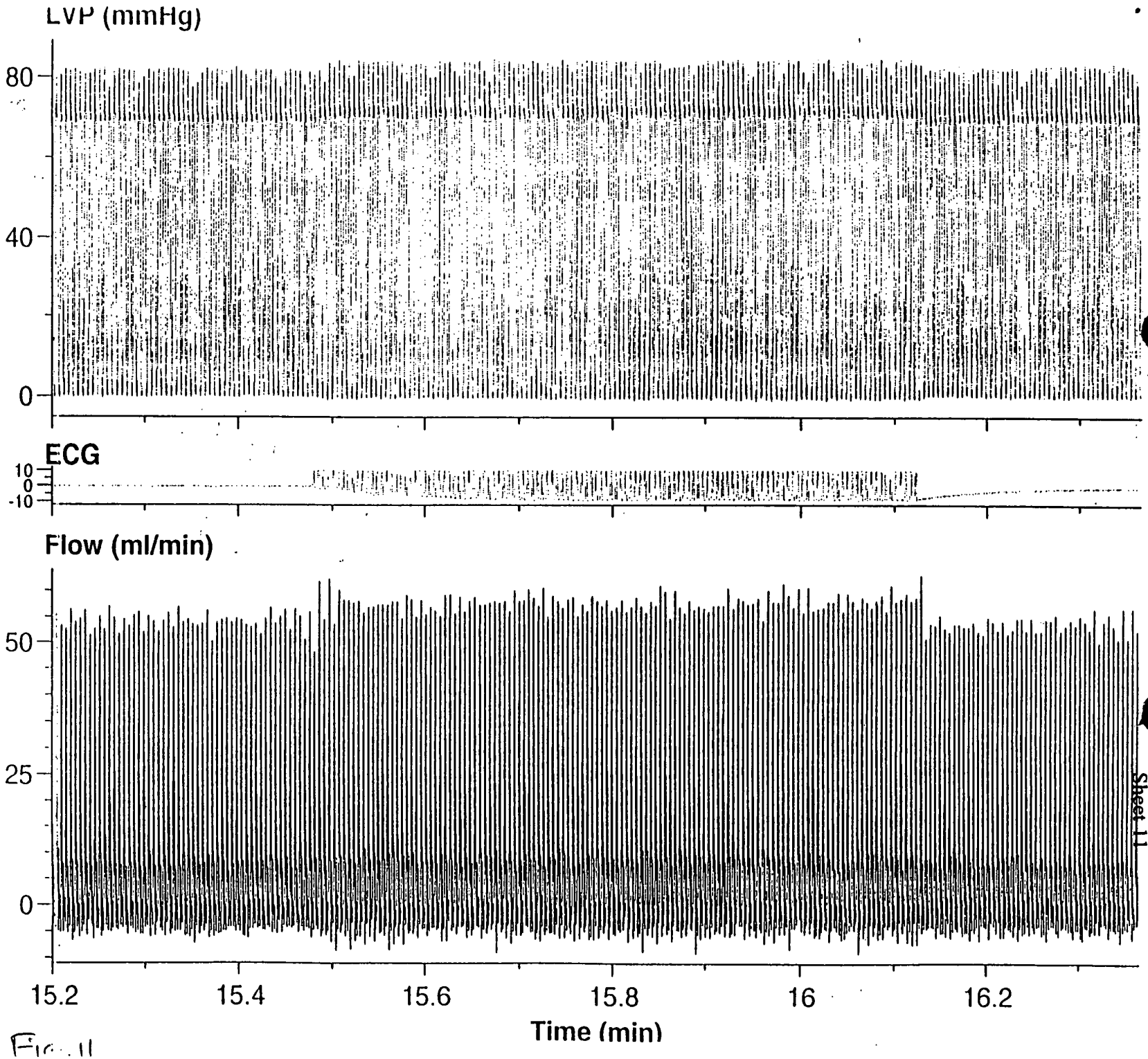


Fig. 11

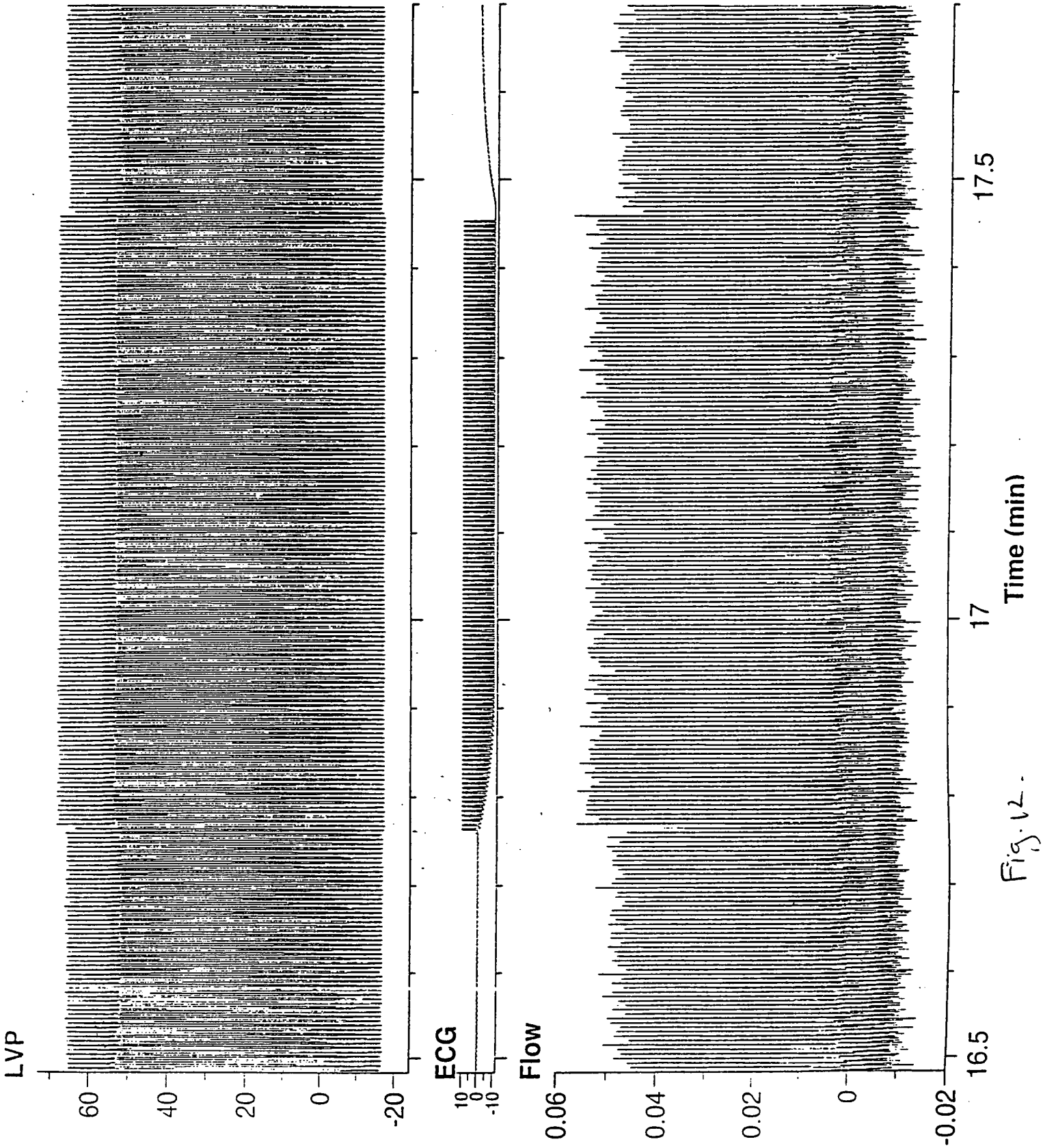
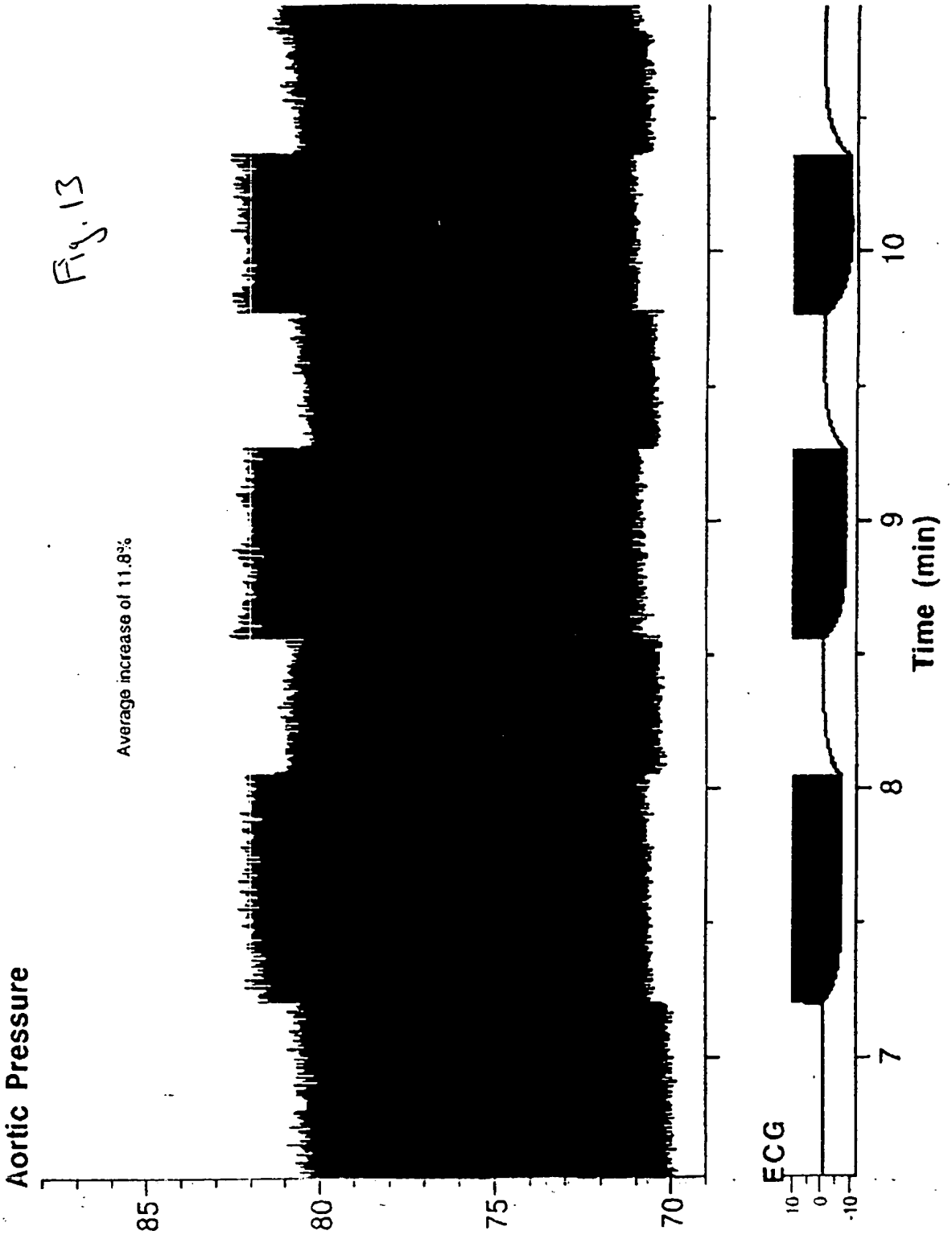

LVP
60
40
20
0
-20
ECG
10
0
-10
Flow
0.06
0.04
0.02
0
-0.02
16.5
17
17.5
Time (min)

Fig. 12.

Fig. 13


Aortic Pressure
85
80
75
70
Average increase of 11.8%
ECG
10
0
-10
7
8
9
10
Time (min)

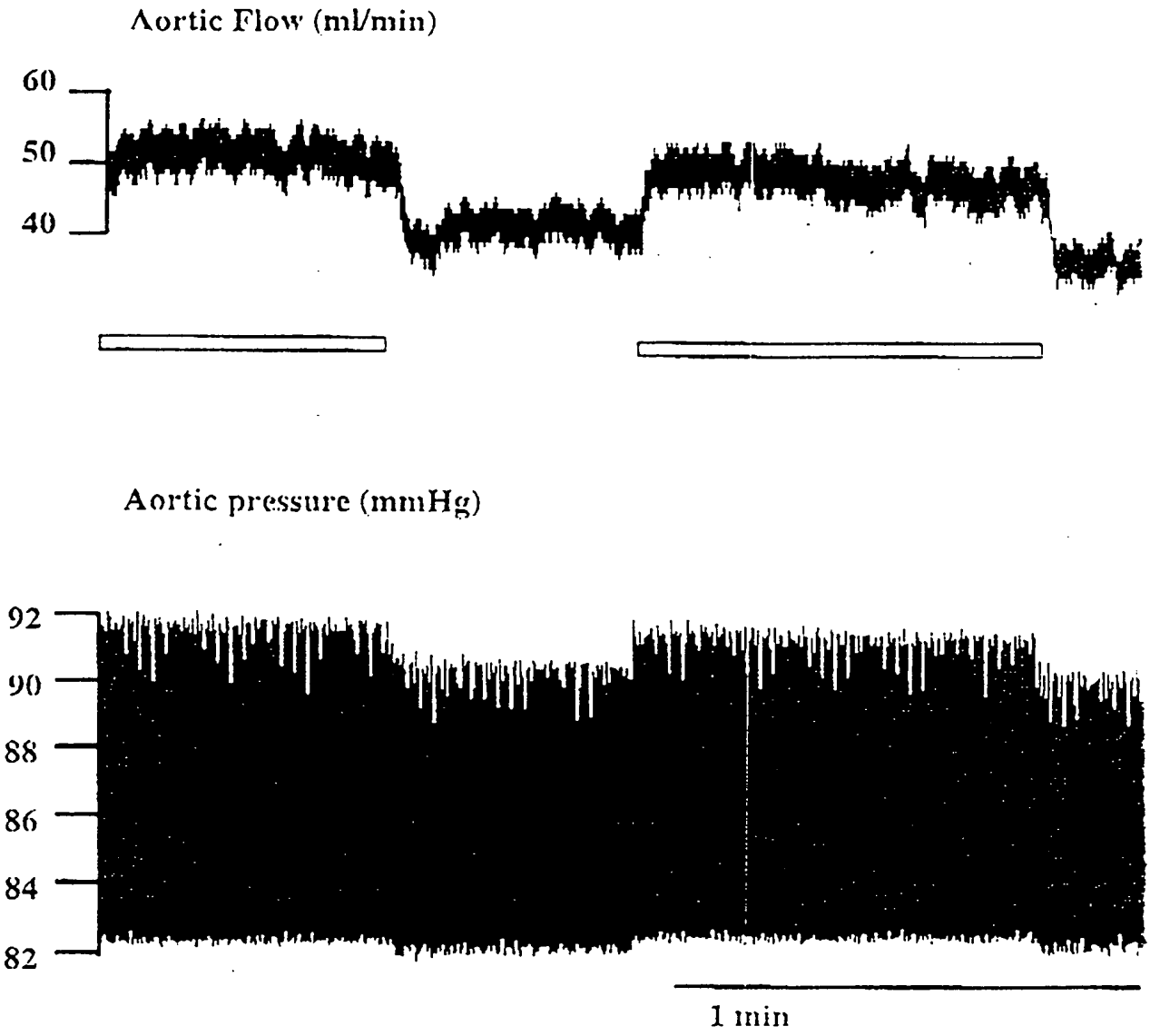
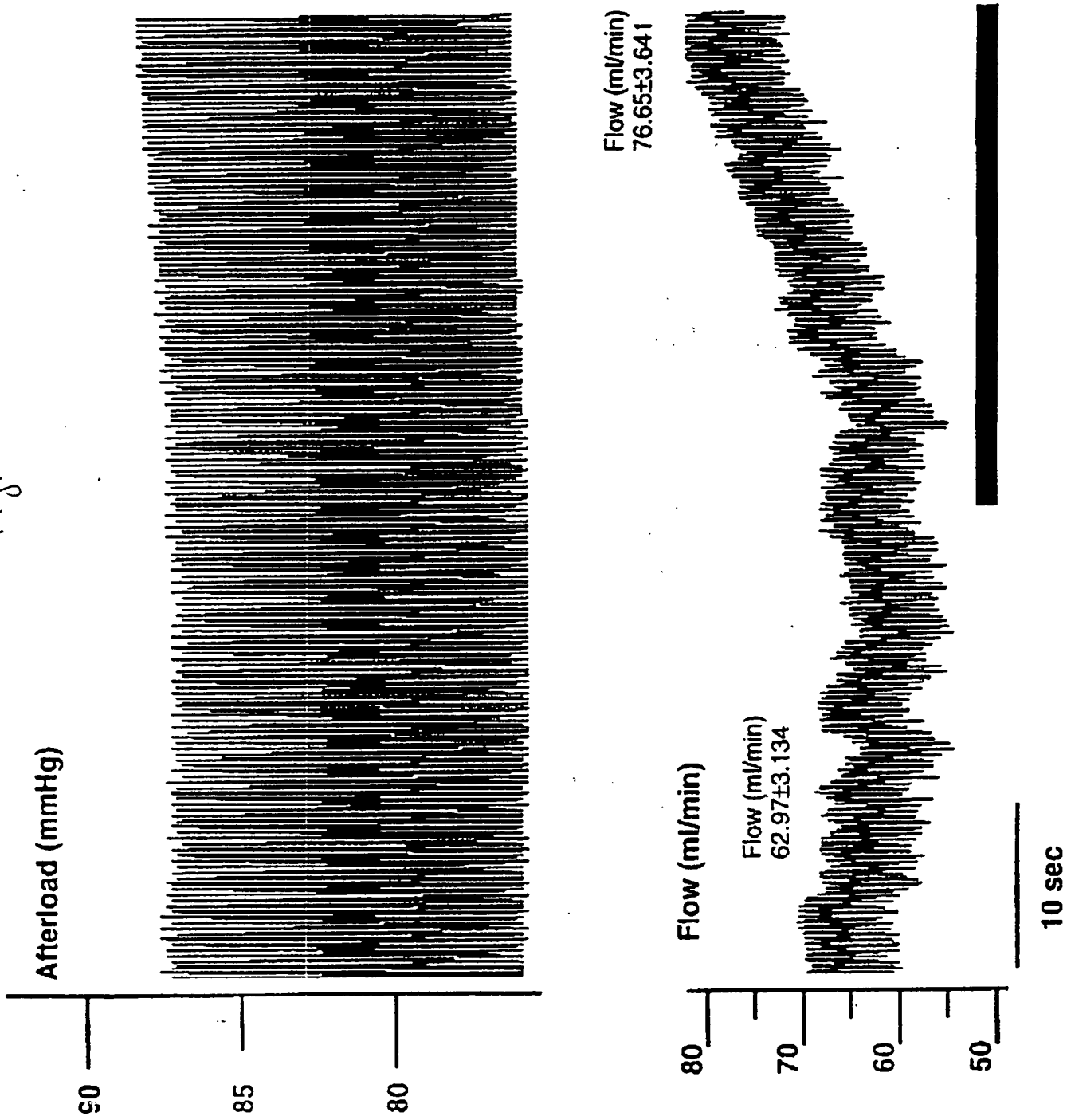

Aortic Flow (ml/min)
60
50
40
Aortic pressure (mmHg)
92
90
88
86
84
82
1 min

Fig. 14

Fig. 15


Afterload (mmHg)
90
85
80
Flow (ml/min)
76.65±3.641
Flow (ml/min)
62.97±3.134
Flow (ml/min)
80
70
60
50
10 sec